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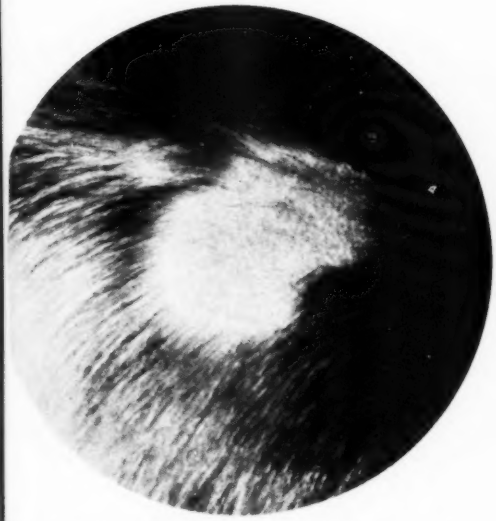

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The Editors of POSTGRADUATE MEDICINE will be pleased to consider original papers in the fields of general medicine, as well as all the specialties, so presented as to be of value and interest to practicing physicians.

Papers should be typewritten, double spaced, and the original, not a carbon copy, should be submitted. Tissue weight paper should not be used. It is suggested that manuscripts comprise a maximum of approximately 3000 words. Authors' full names, academic or professional titles, and complete addresses should be given.

Bibliographies should be kept to a minimum and typed on separate sheets. References should include the author's full name, complete title of article, abbreviated name of journal, volume number, first page and year. References to books, monographs and pamphlets should include the author, title, name and city of the publisher, year of publication, edition and page number of the reference. References should be numbered consecutively throughout the paper and listed in order by number from the text.

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• HEMOSIDEROSIS

Q. What is the treatment for hemosiderosis in a 45 year old man whose chief complaint is extreme weakness? The clinical findings indicate the presence of myocarditis and diabetes.

M.D.—British Columbia

A. The data are insufficient for an adequate discussion of this case.

The term "hemosiderosis" is applied to a condition in which there is deposition of iron-containing pigments in tissues. These deposits occur either locally, as a result of extravasation of blood, or generally through the reticuloendothelial system as the result of numerous transfusions of blood.

The term "hemochromatosis" is applied to a specific disease in which there is abnormally high absorption of iron and extensive deposition of iron throughout the tissues of the body. This condition causes injury to multiple organs such as the liver, pancreas, heart, etc. It is sometimes called bronze diabetes.

Whether or not hemosiderosis can lead to hemochromatosis is still undecided.

The management of general hemosiderosis is secondary to management of the primary disease for which the multiple transfusions are given. There is no treatment for hemosiderosis. The management of hemochromatosis involves appropriate treatment of the cirrhosis, diabetes and congestive heart-failure by means of suitable diet, vitamins, insulin and digitalis. Repeated phlebotomies over a long period may be effective in lowering iron stores in serum and tissues. This may be demonstrated by iron stains of serial sections of bone marrow and liver needle biopsy material, as well as by color index readings and determinations of the iron content of the serum. The lowering of iron stores in tissues, however, does not restore injured organs to normal.

The complaints of extreme weakness, myocarditis and diabetes in the case cited suggest the possibility that hemochromatosis is present.

• VASECTOMY

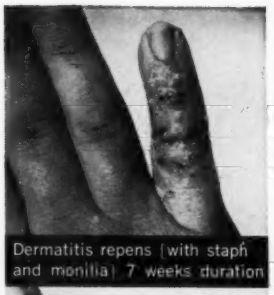
Q. What are the possible complications or sequelae of vasectomy? Should local or general anesthesia be used? (I have been using light injections of PENTOTHAL® sodium.) At what time is a sperm examination indicated to determine the effectiveness of the operation, and how soon after surgery can the patient have sexual intercourse?

M.D.—Puerto Rico

A. Granulomas occasionally occur after vasectomy and ultimately may require epididymectomy. In a few rare instances, canalization occurs and a repeat operation is necessary. Either local or general anesthesia may be employed. Pentothal sodium is perhaps most favored, since it eliminates the mild discomfort that may persist despite local anesthesia. Unless the ejaculum is examined, patients should avoid sexual intercourse for four to six weeks, but examination of the semen 10 days to two weeks after operation usually reveals absence of spermatozoa.

(Continued on page A-20)

new for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions



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References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.; Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr.; Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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• MEPERIDINE VS. CODEINE

Q. In a recent issue of POSTGRADUATE MEDICINE, meperidine was described as having proved four times as active as codeine in suppressing artificially induced cough in cats. Other instances of the effectiveness of meperidine also were cited. I am tempted to substitute meperidine entirely for codeine in cough remedies, especially since it is cheaper. Although both agents produce somewhat similar undesirable side effects, such as respiratory depression and a tendency to addiction, the dosages likely to be used in controlling coughing would not cause some of these side effects. However, I have not been able to find sufficient information on the relative drawbacks of these drugs in regard to side effects. Considering that equal dosages of each drug would be given, could you tell me which drug would be less toxic to children and which would be more likely to induce addiction?

M.D.—California

A. It usually is difficult, if not impossible, to find critical and exact information with respect to the toxicity of drugs for man. Comparisons of two compounds under identical conditions very often are unobtainable. On the basis of objective information, it is almost impossible to answer a question regarding the relative toxicity of meperidine and codeine for children of undesignated age and size. Furthermore, when speaking of toxicity in connection with the narcotic analgesics, it is well to define the term "toxicity." If one is concerned only with the antitussive action of these compounds, all other effects they might produce could be considered side effects or possibly even toxic effects.

Perhaps of greatest concern are those undesirable effects resulting from actions of the drugs on the nervous system, e.g., respiratory depression and tolerance addiction. From this standpoint, meperidine and codeine may be compared best by equating them against morphine. It is generally accepted that meperidine causes less marked respiratory depression than does morphine. Available evidence from both experimental and clinical observations denies the original claims that meperidine lacks such hazard. In infants and young children, as well as in the aged and in patients with expanding intracranial lesions, meperidine may cause a marked impairment of respiration.

Codeine is stated to be one-fourth as depressant to the respiration as is morphine. The degree of respiratory depression does not parallel an increase in dosage. As a matter of fact, large dosages tend to stimulate the central nervous system. Tolerance to codeine develops slowly, and the liability of addiction to this drug is very low. Tolerance to meperidine develops more slowly and not to the same degree as does tolerance to morphine. Moderate physical dependence occurs on continued usage. The liability of addiction is greater with meperidine than with codeine. This undoubtedly is the reason that as an antitussive meperidine has been recommended for only a three to five day course of therapy, and wisely so.

• TRAUMA AND MULTIPLE SCLEROSIS

Q. A 51 year old woman was confined to the hospital for a period of 17 weeks for treatment of an acute episode of multiple sclerosis. About one week after she became symptom-free, she sustained lacerations of the scalp and fractures of the pelvis in an automobile accident. One day following the accident, she had a mild convulsive seizure which lasted about eight minutes and then subsided.

Is there any evidence that trauma in any form could cause an exacerbation of symptoms or precipitate an attack in a case of proved multiple sclerosis?

M.D.—Massachusetts

A. Nonspecific trauma to any part of the body has always been considered a potential exacerbating or precipitating factor in a recurrent or first attack of multiple sclerosis. However, carefully controlled statistical evaluations of the role of many alleged precipitating factors, including trauma, have caused some doubt of this long-accepted association. Relapses in multiple sclerosis occur so frequently without any obvious precipitating cause that the factor of coincidence must always be seriously considered. Nevertheless, some of the statistics (notably, those of McAlpine in the *Quarterly Journal of Medicine*) suggest that the incidence of relapse following injury, infection, surgery, etc. is higher than that which would be expected otherwise.

Incidentally, convulsions which apparently are associated with cerebral plaques do occur in a small proportion of patients who have multiple sclerosis.

What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

CROUP-VIRUS LINK TIGHTENED

American Academy of Pediatrics:

- It has been postulated in the past that viral infections are responsible for a majority of cases of croup. Using tissue culture technics, investigators have recovered several viruses from such patients in recent years. In some instances, an etiologic association between infection with these viruses and the croup syndrome has been established.—Dr. Henry G. Cramblett, State University of Iowa College of Medicine, Iowa City.

- A follow-up of seven infants operated on for coarctation of the aorta and patent ductus arteriosus showed that four of the patients had no hypertension and no clinical evidence of additional cardiac defects after one to four years. This experience reaffirms the conviction that early surgical intervention is feasible and lifesaving.—Dr. M. Remsen Behrer, Washington University School of Medicine, St. Louis.

- The inordinate use of tranquilizers in adults has overflowed into the field of pediatrics. In children, tranquilizers do not have the same degree of beneficial effects that they apparently have in adults. In children with milder behavioral problems, however, the tranquilizers are beneficial. They are useful primarily as an adjuvant to other more basic approaches, such as the removal of social and emotional problems. Some of the stimulants, such as those of the amphetamine series or of the monamine oxidase inhibitors, may be more valuable in decreasing hyperactivity of a child than are, perhaps, the tranquilizers.—Dr. Meyer Perlstein, Cook County Hospital, Chicago.

- A 27 year study of the growth and development of 134 children from the fetal period to their eighteenth year underscores the need for caution in trying to identify the basic pattern of a child's growth on the basis of progress during the early months. Different individuals follow a variety of patterns.—Dr. Harold C. Stuart, Harvard Medical School, Boston.

HEREDITY AND PROSTATE CANCER

American Society of Human Genetics:

- In a study of the families of 288 men who died of prostate cancer, 15 male relatives were found to have died of the same disease. This was three times the number of deaths from cancer in a control group. Female relatives of the study group showed no more cancer deaths than did the controls.—Dr. Charles M. Woolf, University of Utah College of Medicine, Salt Lake City.

Improved results in stomach cancer

Omaha Mid-West Clinical Society:

• While a gloomy prognosis has regularly been associated with cancer of the stomach, several hopeful aspects deserve emphasis. At the present time approximately 13 per cent of all patients who enter Massachusetts General Hospital with this disease are alive five years later. Analysis of the cases indicates that this improvement is due particularly to early diagnosis (special attention being paid to patients with supposedly benign ulcers, polyps or pernicious anemia), to more frequent operations, and to more radical rèsections. For cancer of the distal stomach, subtotal distal resection is considered adequate; large cancers of the fundus or entire stomach are treated by total gastrectomy, splenectomy and hemipancreatectomy.—Dr. Claude E. Welch, Massachusetts General Hospital, Boston.

Schools "ignoring" general practitioners

Second World Congress on Medical Education:

• The demand for competent general practitioners has been largely ignored by some of our medical schools. It is wasteful and foolish to tailor the curriculum of our medical schools to the theory of research rather than to the practice of medicine. It seems much more logical first to train good doctors; then those who have the flair could continue in research with a greatly improved foundation and better understanding.—Dr. Malcolm E. Phelps, El Reno, Okla.

• Medical students throughout the world are overburdened with theoretical teaching. Interns should be allowed to devote at least two months to practical work in hygiene and preventive and social medicine. Even a general practitioner in rural areas must participate in preventive work. He should be trained in that area before establishing himself in a position.—Dr. R. M. Tadic, Institute of Hygiene, Belgrade, Yugoslavia.

• To be a good investigator or teacher, one must possess and develop enthusiasm, curiosity, constant devotion, habit of accurate thinking, tendency to form one's own judgment without mere repetition, idealism, perseverance, generosity, faithful devotion to truth, and a spirit of justice.—Dr. Bernardo A. Houssay, National University of Buenos Aires Faculty of Medical Science, Buenos Aires, Argentina.

Genetics outweigh environment

American Heart Association scientific sessions:

• An investigation of the roles of heredity and environment in determining circulating lipid levels in healthy persons was conducted among 2500 persons living in "highly urban" Manhattan and "semirural" Staten Island. The stressful life of the Manhattanites was not reflected in cholesterol levels. However, strong positive and statistically significant correlations existed in cholesterol levels of father and children, mother and children, and sibling and sibling. It was concluded that cholesterol levels are determined by genetic factors and modified to only a limited extent by the environmental influences.—Dr. Louis E. Schaefer, New York.

• Selective hypothermic arrest of the human heart, using cold blood until the temperature is reduced to 17° C. or below, seems to offer several advantages over arrest with potassium citrate. It provides complete arrest yet obviates the deleterious effects of hypoxia by allowing for intermittent coronary perfusion. Energy requirements are reduced to 25 per cent of normal, thus greatly lengthening the duration of safe arrest.—Dr. Vincent L. Gott, University of Minnesota Medical School, Minneapolis.

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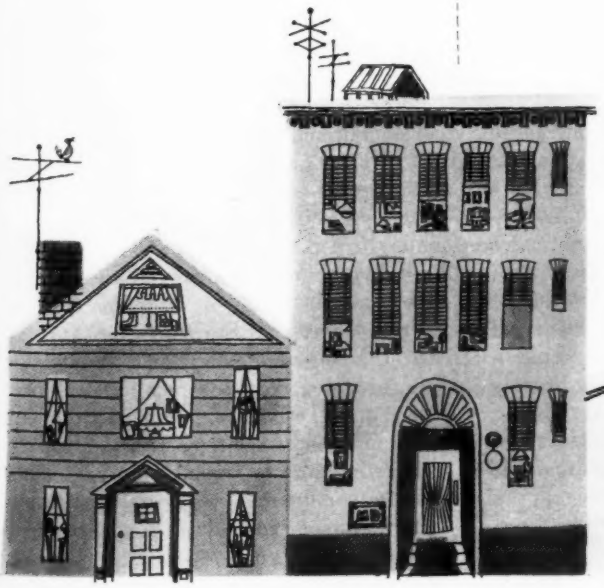

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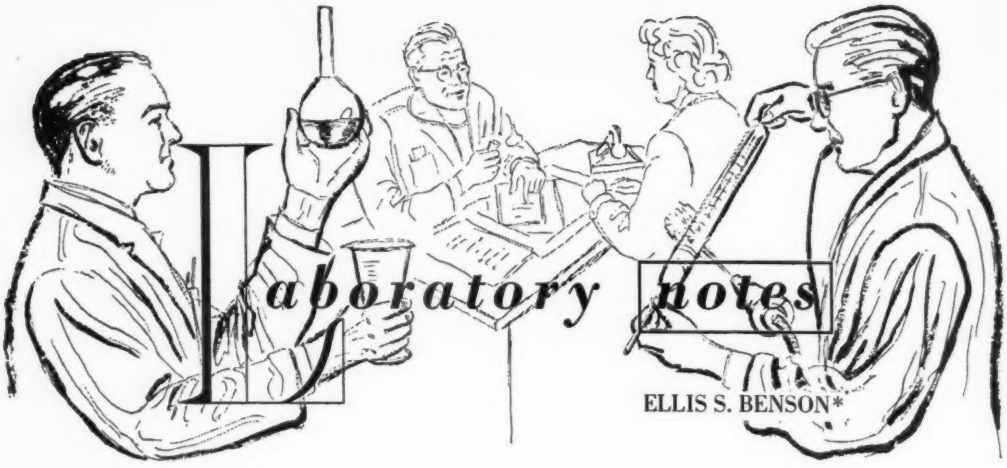

ELLIS S. BENSON*

Diagnostic Tools for Case Finding in Hyperparathyroidism

In a fascinating paper entitled "A page out of the history of hyperparathyroidism," Fuller Albright[1] recounted the events that led to the first surgical removal of a parathyroid adenoma by Mandl in Vienna a little over 30 years ago and to the first diagnosis and subsequent investigation of a patient with primary hyperparathyroidism by DuBois and others in this country. The two subjects, Albert of Vienna and Charles Martel, an American mariner, had osteitis fibrosa cystica, a skeletal manifestation of the disease, in an advanced stage. The condition was so advanced in fact that, in Albright's words, the patients were "rapidly approaching the jellyfish, skeletonless stage." These historically important cases illustrate the fact that hyperparathyroidism initially was described primarily in terms of its skeletal features. Subsequently, its renal manifestations—nephrolithiasis and nephrocalcinosis—gained emphasis, and it became clear that the condition was not a rare disease and that prolonged hyperparathyroidism readily led to the tragic consequence of permanent, severe impairment of renal function. Early diagnosis makes it possible to avoid through surgical intervention this irreversible complication, but the vague and varied symptomatology of the early stages makes this a disease in which to an almost unparalleled extent a special search is required. Fortunately, the biochemical findings in serum and urine are sufficiently characteristic to permit an early diagnosis to be made.

Diagnosis of hyperparathyroidism should be considered and sought for in the following:

1. All patients with renal stones, especially if the stones are found to contain significant quantities of calcium or phosphorus. Approximately 4 per cent of patients with renal stones have hyperparathyroidism,[2,3] and in those with recurrent stones the incidence may be as high as 15 per cent.[3]

2. Patients with nonspecific skeletal disorders such as generalized demineralization.

3. Patients who have vague gastrointestinal complaints not associated with definable gastrointestinal disease, such as anorexia, nausea, vomiting, abdominal pain and constipation. One should be particularly suspicious of pa-

(Continued on page A-42)

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

in the formula base has obvious advantages to the physician, who must decide what each infant needs, and when changes are indicated. An evaporated milk formula is a prescription formula, permitting the physician to adjust

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tients who have complaints resembling those of duodenal ulcer which fail to respond to or are aggravated by conventional ulcer dietary regimens. (Such patients are those who state, for example, that "milk somehow makes me feel worse in a little while."[4])

On administration of PARATHORMONE®, the following changes take place in sequence:[2] (1) an immediate transitory increase in urinary excretion of phosphorus; (2) a fall in the serum level of inorganic phosphorus; (3) a rise in serum calcium; (4) an increase in the urinary excretion of calcium. The biochemical abnormalities of primary hyperparathyroidism are strictly in keeping with these hormonal effects; thus, elevated serum calcium, decreased serum inorganic phosphorus, and increased urinary excretion of calcium are the diagnostic triad of the disease. If these determinations were simple and relatively free of technical and interpretative errors, nothing more would need to be said on this subject. Since this is unfortunately not the case, I will review briefly some of the pitfalls encountered in these biochemical determinations.

In interpreting *serum calcium* determinations, the following considerations should be kept in mind:

1. The normal range is narrow. Ninety per cent of serum calcium levels in normal adults lie in the range of 9.5 to 10.5 mg. per cent.[5] In some patients with definite parathyroid adenomas, the elevation in serum calcium is only moderate (10.5 to 11.5 mg. per cent).[2] This circumstance illustrates the need for precision in this measurement if it is to be useful. One must also keep in mind that in children serum calcium normally falls in the range of 10 to 11.5 mg. per cent, and in infants, 10.5 to 12 mg. per cent.

2. Multiple determinations may be required to evaluate properly the serum calcium. In a series of 25 patients with parathyroid adenomas, nine had normal or borderline serum calcium levels (up to 10.8 mg. per cent), but on repeat determinations seven of these at one time or another had values which were above 11 mg. per cent.[4]

3. Because this is one serum constituent in which a high degree of precision of measurement is necessary, the laboratory should be able to vouch for the precision and accuracy of the determination. Unfortunately, surveys show wide variations in results obtained from different laboratories and, generally, a poorer performance on this measurement than on most other serum constituents.[6] This has been due partly to complex methodology. The large number of methods for determining serum calcium which are published each year are testimony to the fact that none has been so simple and reliable as to gain wide acceptance. Recently developed methods, using titration with EDTA, seem to answer the need for a rapid, accurate determination.* Whatever method is used should be carefully monitored by quality control methods.[8]

The combination of elevated serum calcium and *decreased serum inorganic phosphorus* is sufficiently unique to be of great diagnostic significance. This combination serves for the most part to distinguish primary hyperparathyroidism from other metabolic diseases of bone. On the other hand, when renal insufficiency is present, the inorganic phosphorus may be normal or even elevated. The normal range in adults is 2.5 to 4 mg. per cent.[9] In suspected cases in which normal values are obtained, the determination should be repeated, since in many instances patients with proved adenomas have had levels ranging from normal or even high to definitely low on repeated measurements.[4,9] Patients should be in the fasting state (an overnight fast proves sufficient).

Particularly in obscure, latent or atypical cases (those in which the serum calcium is normal or only slightly elevated), determination of *urine calcium excretion* may be of great help in establishing the diagnosis.[2] It seems to be increased in the early, mild cases in which a complete cure may be achieved. For a proper evaluation of this excretion the patient must be on a constant low-calcium diet,[2†] and repeated quantitative determina-

*We are using successfully one of these described by Appleton et al.[7]

†See page 75 of this reference.

(Continued on page A-44)

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tions of urine calcium must be made. Unfortunately, most quantitative methods for urine calcium are either very time-consuming or very inaccurate, or both.

A convenient, rapid screening test which is semiquantitative is based on the use of the Sulkowitch reagent,[10] which is composed of 2.5 gm. oxalic acid, 2.5 gm. ammonium oxalate, 5 cc. glacial acetic acid, and a sufficient quantity of distilled water to make 150 cc. Five cubic centimeters of this reagent is added to a test tube containing 5 cc. of urine, the pH of which has been adjusted to pH 5 with acetic acid. The tube is inverted and the results read as follows: 0 = no cloud in two minutes; + = fine cloud in no more than 30 seconds; ++ = moderate cloud in more than 30 seconds; +++ = moderate cloud in less than 30 seconds; ++++ = curdlike cloud immediately. A control test is run in the same manner, using a normal urine, which should test + to ++. A negative or low result (trace to +) tends to exclude hyperparathyroidism except when definite renal insufficiency is present. (A positive result usually excludes hypoparathyroidism.)

An elevated serum alkaline phosphatase is not a sign of hyperparathyroidism per se, but of bone disease. It is elevated only in the minority of patients who have pronounced skeletal involvement; therefore, it is of limited value in the diagnosis of this condition.

Recent efforts have been made to introduce new diagnostic tests in order to detect with accuracy the earliest, mild cases in which complete cure can be expected and to help resolve the atypical cases in which the traditional diagnostic criteria (elevated serum calcium, decreased serum phosphorus, increased urine calcium) are lacking or indefinite. Some of the more successful of these have been tests designed to measure the tubular reabsorption of phosphate by the kidney.[9] These tests are complex and specialized and will not be described here.

More useful as a diagnostic screening method in the type of search necessary for early diagnosis of hyperparathyroidism is the phosphate clearance test.[11] This test requires a carefully timed collection of urine over a period of two to four hours and measurement of urine volume, urine phosphorus concentration, and concentration of serum inorganic phosphorus at the midpoint of the urine collection period. The patient should be given enough water before and during the test to promote a urine output of 5 to 10 cc. per minute. Phosphate clearance (Cp) is estimated by use of the formula: $Cp = \frac{V \cdot [P]_U}{[P]_S}$ where V is volume of urine excreted per minute, $[P]_U$ is urinary concentration of inorganic phosphorus in milligrams per cubic centimeter, and $[P]_S$ is the serum concentration in milligrams per cubic centimeter. Twenty-five normal adults had Cp values of 6 to 16 cc. per minute, whereas five of six hyperparathyroid patients had values above 16 cc. per minute (the range was from 18 to 40 cc. per minute).[11] Since phosphate clearance is markedly influenced by variation in phosphorus intake, the test should be performed in the forenoon on patients in the fasting state.

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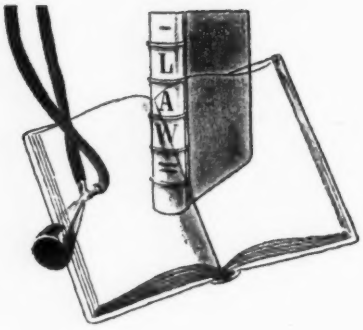

Forensic Medicine

The Judge Looks at the Impartial Doctor

ARON STEUER*

New York

DOCTORS as witnesses are exactly the same as doctors regarded as people. They have the same attributes in the courtroom as they have outside of it. The vast majority are honest and know what they are talking about. A somewhat smaller majority are convincing in their presentation. This is the credit side. On the debit side is that few of them are disinterested or objective. The physician finds himself in court due to one of two relationships: He has either treated the plaintiff professionally or has examined him for the purpose of testifying. In the first situation there is a personal relationship of varying intensity. But in almost every case there is some degree of interest in the patient's welfare. In addition, the more serious the injury, the greater the skill the physician demonstrates in the result; or where, despite the treatment, the result is unfortunate, the more easily is it explained by a grievous condition following the accident. Doctors who are uninfluenced by these considerations may sometimes be found, but it is rare.

The medical man who testifies but does not treat is likewise subject to influences which affect his objectivity. Sometimes these are financial. An extreme example once came to my attention. An eminent specialist in the winter of his career accepted a very substantial retainer from a labor union. It enabled him to give up the bulk of a large practice which his years were making somewhat of a burden. This ideal situation soon proved illusory. The doctor believed he was being retained to advise on conditions in the industry as affecting the health of the workers. He soon found out that his chief occupation was to substantiate claims for workmen's compensation and to lend the prestige of his well-earned reputation to their support. And he discovered that he could be as impartial or objective as he wished, just so long as he found that the union member's condition was a result of an industrial accident. Although he found it out soon, it was nevertheless too late, and the twilight of his career was filled with extraordinary conclusions based on very ingenious theories.

The net result is that too often in the trial of a case involving medical questions, the

*Justice, Supreme Court of the State of New York, New York.

(Continued on page A-54)

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trier of the facts, be it judge or jury, is faced with professional testimony which can not be reconciled. Of course this is not the situation in every case. If a man's finger is sheared off in a collision, there is not much room for professional dispute as to either cause or consequence. Nor is there always serious difference in cases that might provide a forum for it. I have, many times, heard one doctor's testimony endorsed by the expert on the other side, and fairly often lawyers have forborne to put their own expert on the stand because they were satisfied with the accuracy of the testimony given by the doctor called by the other side. I can remember an incident when a leading authority on trichinosis went out of his way to endorse the testimony on that disease given by a Syrian doctor unknown to him. Also there are cases where a difference of opinion is warranted.

With all of these cases excluded there remains a large number—just how large it is impossible to say. But the number is sufficient to arouse the conscience of the community in many of the several centers of litigation in this country. This feeling of indignation occurs because difference of opinion is expressed where none is justified. To this can be traced the formulation of the various methods of providing impartial medical testimony now existing or in process of formation in various cities throughout the nation. These plans differ with different jurisdictions. It is not the purpose of this article to describe any of these plans. Presumably, the reader is acquainted with the basic features of one or more. Suffice it to say that practically every plan provides for the designation of an impartial expert in the specialty under consideration and for his appearance as a witness.

For a plan to have any value, the jury must be told the facts with regard to how this impartial expert comes to be there. If this information is kept from them, then the court-appointed physician is just another medical witness, and his testimony becomes merely a cumulative factor in the confusion already created. This is especially evident in cases where each side calls several experts of its own. It is too much to expect that the jury will recognize the superior position of the court-appointed doctor by a recital of his qualifications. A clever lawyer can sometimes make even a damning professional history look good; i.e., a simple question like, "And have you been an assistant resident surgeon at St. Elizabeth's hospital for the past seven years?" followed by a triumphant look at the jury who do not realize that this is far too long a period for a position of this grade. In fact, as it takes longer to pronounce the title than it does to say diplomate in surgery, the uninformed will often take the former to indicate superior accomplishments. I have also seen much made of poorly paid political jobs with high-sounding titles.

Now what is the effect of informing the jury that the doctor is a court-appointed and therefore impartial expert? In the overwhelming majority of cases, it is the effect expected—the jury accepts his testimony as true. To many people, this is a cardinal defect. Everyone can see that it would be regarded with hostility by those members of the fraternity whose aim in life is to put something over. But they are joined in this by many whose motives are more praiseworthy. Strangely enough the Anglo-Saxon concept of a lawsuit is not primarily a search for the truth. Instead, it is *a correct evaluation on the evidence presented*. While often parallel, these concepts are distinct and different. Ours is an instance of the procedure shaping the concept. We have the adversary system in which each contestant presents his claim and the arbiter decides not on what he knows or can learn for himself, but on what is presented to him. Incidentally, this system is basically the concept of the free man—a distrust of all officialdom. Where decision is made on the basis of the record presented, it can be reviewed indefinitely, whereas if it is the consequence of individual inquiry the result is bound to be affected by subjective influences.

It cannot be denied that a witness chosen by the court does violence to the theory of adversary proceedings. It is true that the expert is not appointed by the jury but rather by an authority engaged in the same aim as

(Continued on page A-56)

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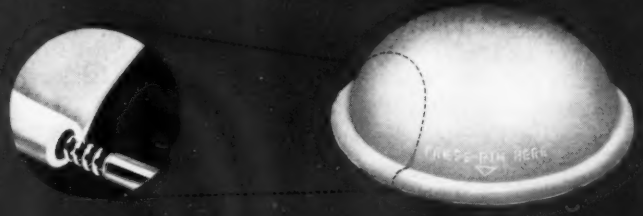

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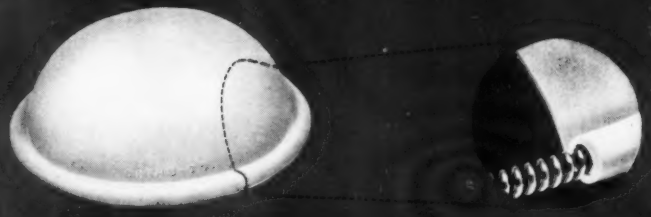

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that of the jury and which the latter has every reason to believe would exercise the same care in selection that they themselves would employ if they had both the power and the facilities for choice. In effect, and to a large extent, the jury is induced to deputize to the doctor their prerogative and duty to decide, at least in a branch of the case. Is such a material variation to be accepted without danger to the entire structure of the law?

While our concept is that of a contest in form, we have never considered that a lawsuit is a game; that is, a stylized contest dependent on fortune or certain skills. When experience with the rules indicated injustice, the rules were changed; when situations arose that the rules could not cope with, new rules were formulated. We have such a situation now. Two factors have had great influence in bringing it about.

Foremost is the prevalence of insurance. It is a fiction of our law that the presence or absence of insurance is a factor not to be considered. It is forbidden to mention the subject and the very word causes the courtroom to stir with apprehension of a mistrial. Yet in virtually every case the jury is in some way told that there is insurance or that the defendant is a financial giant strong enough to be a self-insurer. This has had an immeasurable effect on our law. The general rule that liability is only involved through fault receives lip service only. The real rules are: (1) Was the plaintiff hurt? (2) Is he the kind of person who ought to recover? (3) Was the accident altogether his fault? If the answers to the first two questions are positive and the last negative, the chances are he will get a verdict. The only obstacles are an extremely conscientious jury and an unusually able and influential judge. Before insurance was well-nigh universal this was not the case, nor is it the case today in the rare instance where the defendant is uninsured. In such cases, most juries are careful not to inflict damages unless there is clear liability according to law. But insurance has conditioned most jurors and not a few judges along the line of the following reasoning (not necessarily consciously recognized): An insurance company exists to pay claims for which it collects premiums; the plaintiff was hurt; the insurance company seeks to escape payment by virtue of purely fortuitous circumstances over which it had no control and which reflect no virtuous action on its part; so, why should it benefit from these circumstances?

To illustrate the foregoing, consider the following case: A painter is working on a scaffold. One of the supporting ropes breaks and the resulting fall leaves the painter a hopeless cripple for life. The factual issue in the case is whether the defendant, who supplied the rope, had reason to know it was defective. Now if the defendant were to be responsible personally, it is only fair that he should pay if he consciously or recklessly provided an unreliable rope. But it is just as unfair to ruin him financially if he were entirely innocent and if the break of the rope could not be attributed to his fault. Under these circumstances, a jury will consider the question with great care. But if the paying party is an insurance company, the approach is altogether different. It did not select the rope. If it happens that the man who did supply it did all that was humanly possible in the way of care, that is just the insurance company's good luck. Few juries will let that good luck prevail against the painter's tragic misfortune. If there is any possible field for controversy, the question will almost inevitably be resolved in favor of the plaintiff. Whereas if there were no insurance, the merits would play the dominating role.

The emphasis in litigation accordingly has shifted from the question of liability to the question of damage, and the medical testimony assumes ever-increasing importance.

Secondly, we have the changing economic situation of the bar. Professional fees are among the later items to adjust to economic conditions. While in some branches of practice, where the return is largely influenced by the amount involved, the inflationary course of the past decades has been reflected in lawyers' fees, in many other branches it has not. This is particularly true of the local or family lawyer, the man who draws leases, wills

(Continued on page A-58)

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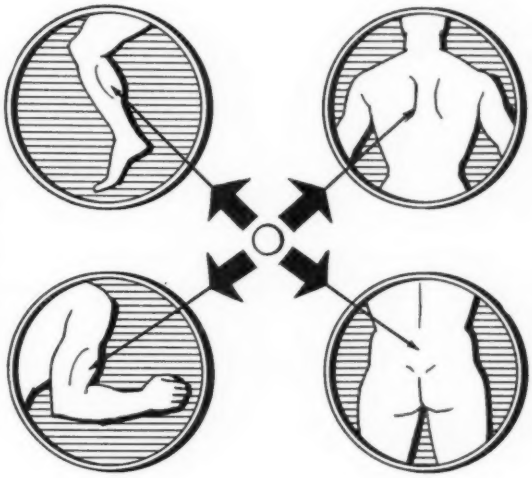

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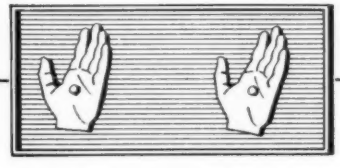

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and contracts and performs the multitudinous services that are required. Today that man lives on one or two or three negligence cases which come to him in the course of a year by reason of his contacts. Unless these cases are won, or at least a majority of them, his economic position will not be good. Often the same is true unless each case is made to return its maximum potentiality. Therefore, with so much depending on the medical testimony, he will not be remiss in seeking the doctor who will give the most favorable testimony. In this connection, knowing that the reputation, standing or honesty of the doctor will seldom be questioned, he may not be particularly squeamish in his choice. The insurance companies fight fire with fire. They have even been known to start the first fire on the theory that the best defense is a vigorous offense.

These are the conditions that the law faces. It can no longer rely on the adversaries presenting the facts and hoping thereby to reach truth. The adversary system was never considered sacrosanct. If six witnesses testify that the traffic light is on the north corner and six others that it is on the south corner, the court always had the power to take the jury to the scene to see for themselves. Under a strict limitation to the evidence presented, this would not be permissible. The fact that the right is unquestioned shows that our concept has sufficient flexibility to allow some exceptions.

It is true that the jury to an extent delegates its powers when it accepts the impartial expert's testimony. But there is no other way. A jury cannot be expected to absorb a medical education even if practical limitations of time would allow it. Therefore, no jury decision on a basis of which contention is correct can ever have a secure foundation. On an *ad hominum* basis, judging the value of the testimony by the impression created by the witness, we have already seen that the most important index, professional qualification, is useless to the uninitiated. On this facet, the jury is inclined to follow the legal fiction that any holder of a medical degree is competent to answer any medical question and to express an opinion on any phase of the science. Fortunately, the real specialist will often refuse to express an opinion outside his specialty. But unfortunately, the exact opposite is the case when the witness' main qualification is his willingness to testify. As far as the general impression is concerned, we know only too well the qualities which produce it and that they can be present to the exclusion of others of more value. The credit given an opinion by a jury is measured by the thespian quality of the witness.

The net result is that in the bulk of our litigation, the issues that have assumed the greatest importance are being decided on a haphazard basis, because ascertainment of the truth is beyond the capability of the deciding body. That this situation should be tolerated merely because correction would require a change, even though basic, is to attribute to our law a static quality preliminary to mortification. But as long as the final stage is relegated to a time beyond the immediate future, the tendency of a large portion of the bar is to enjoy the benefits of present havoc and let posterity deal with the deluge as best it can.

And so the opponents of impartial testimony fight a rear guard action. In this they have set up several redoubts. Among the first is that the mechanics of the system, as worked out, prevent its adoption in all but major centers of population. The fact is true although the objection is unsound. The plan presupposes a medical aristocracy, a body of acknowledged experts of sufficient number that service on the panel should not be so frequent as to be a burden. The number of communities containing such a group is quite limited. But the objection is to the effect that if the plan cannot work everywhere, it should not be adopted anywhere. In a community where everyone knows everyone else, the reputation of the testifying doctor is generally known. While this is a meager safeguard, it does to an extent prevent outright charlatanism. In the large community even this protection is lacking. It seems a bit farfetched to argue that because it is, no other should be enjoyed.

(Continued on page A-60)

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Another bastion of argument is that the plan carries within it the germ of self-contradiction. This is worked out as follows: The saving grace of the plan is that it does not take from the jury its power to decide, as it is permissible to contradict the impartial expert; but his aura of court approval makes it difficult to the point of practical impossibility to do so. The conclusion, then, is that the permission to contradict is, in most cases, an empty privilege, so the plan, dependent for its legality on that privilege, is contradictory. This is, in a way, true. That is the object of the plan. If the expert's testimony represents an impartial exposition of the recognized medical view, what objection can there be to its being nearly impregnable? Granted that things are not always what they seem, it should take more than a glib testifier and a lawyer with an untiring larynx to show that they are not. The safeguards of permission to show that the expert is wrong or biased should be all that is needed. The difficulty of proving either of these lies not in the accolade given by the court, but that in most cases it just is not the fact.

Lastly, the argument is: Who says the expert is impartial or an expert? This argument does not, as it might appear, attack the panel method of selection or the designation to the panel. The attack on impartiality is based on the effect on the panel doctor of the physicians who have already expressed opinions in the case at the behest of one side or the other. It is claimed that there will be a tendency on the part of the expert to agree with the more eminent of these and, in other cases, a reluctance to disagree with personal friends or influential doctors. It must be admitted that such possibilities exist. The panel system reduces to a minimum the chances of their becoming operative. The only possibility of total eradication is to remove the human element from court trials completely. This is an accomplishment to which we are not even close. The resulting defect is one of the elements with which we have to contend in every field of human endeavor.

Likewise, the contention in regard to the expert's ability is not a direct attack. No one has yet presumed to question the qualifications of the men appointed to the panels. Instead, it is pointed out that there are several areas of controversy in medicine. To take an important instance in litigation, as regards many abnormalities, there is less than accord as to whether they can ever be attributed to trauma. In certain of these fields the cleavage of opinion is so sharp that there are recognized experts on both sides of the question and adherents form separate schools of thought. The impartial expert can be associated with only one school. The side of the case which is contending for the opposing school is practically doomed to defeat before it starts. And, secondly, there is the perennial argument that the entire body of medical opinion has been shown to have been in error in the past, and the name of Louis Pasteur is mentioned to present an irrefutable example.

To the first proposition, the answer is that when there are such variations of opinion, each well backed by solid protagonists, the impartial expert would be the first to admit it. If the matter is so controversial that any opinion must be qualified beyond the limits of reasonable certainty, the condition or its cause becomes unprovable. It was never the law that 12 men in a jury box by some undetermined thaumaturgy suddenly become imbued with the equipment to resolve what has baffled the scientific world for generations. A doctor in the course of therapy must occasionally adopt one of two conflicting theories, so he takes the path that he finds most appealing to his reason. The law is under no such necessity and faces no such dilemma. It determines that the fact cannot be proved, just as many facts cannot be established because they are lost in the mists of time or for other more mundane reasons. To take a concrete example, there is professional doubt as to whether an epileptic condition can be attributed to a trauma where certain symptoms do not appear until years after the accident. If it be established that this professional doubt is bona fide, the jury, surely, cannot be called on to determine it. The party making the claim just cannot substantiate it even though one or

(Continued on page A-62)

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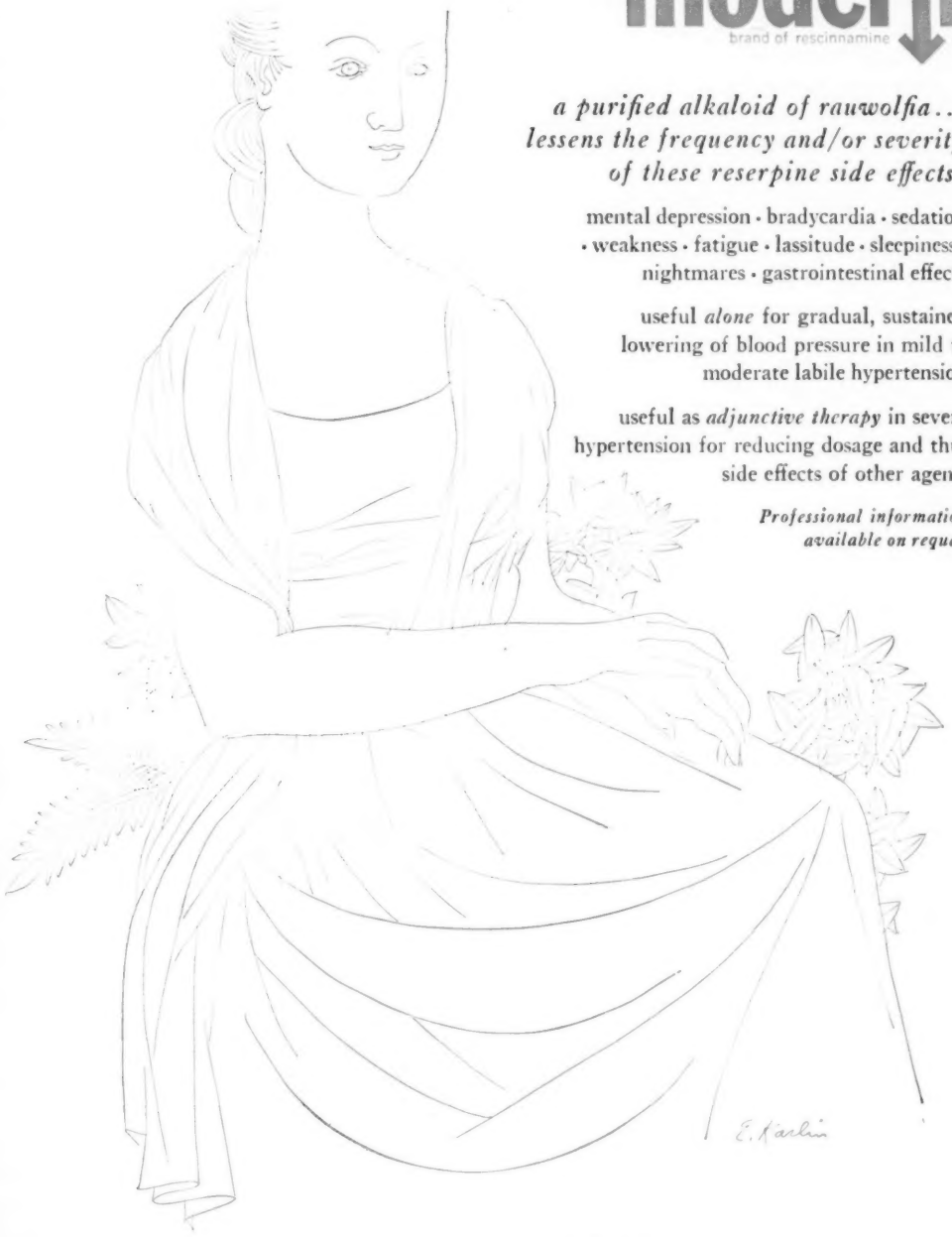

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more reputable physicians are more inclined to the belief that the accident is the producing cause of the injury. Obviously that is and must be the law. But the very presence of this argument, the mere fact that it is advanced by responsible practitioners, shows the extent to which in practice a prominent landmark in the law can be lost sight of and the way along which economic pressure is forcing us.

The final argument associated with the mistakes of science is similarly answerable. No one can claim that the science of medicine sprang fully equipped upon the earth. Its whole history is the correction of misconceptions by the discovery of additional facts and the perfection of technics by the elimination of dangerous or harmful practices. Nor can it be denied that at each stage of its career medicine was practiced by men who accepted the current beliefs, the false along with the true, and treated according to their approved practices, some of which were later to be found virtually lethal. Nor have we any reason to believe that today's theory or practice represents the last word. Actually, we sincerely hope that it does not, and a large sector of the medical profession is engaged in an effort to find improved substitutes for practically every opinion now held. But who is to decide what in our present beliefs is valid—those normally qualified by training and study or those whose sole inspiration is ignorance? The very men who advance this contention that because science changes its tenets, its findings are always questionable, would abandon it if they were required to put their faith to the test. Would any one of them submit to a jury of laymen the issue of whether he himself should undergo an operation because medical opinion was divided or subject to being proved wrong by future generations?

These are the problems that a judge contemplates when faced with impartial medical testimony. How every judge will meet them, I do not know, nor can I even guess. Judges, like doctors, are not a prototype and conform to no pattern. We do what we think is right and agree with one another to the extent that we can. For my part, I believe the plan tends to reduce the effect of charlatanism, to drive quackery from the courts, and to place in their stead that degree of positiveness which in an imperfect world is the substitute for truth. So that consequently to the limit that the law permits, it should receive encouragement and support.

MEETINGS and Postgraduate Courses

BAHAMAS CONFERENCES, NASSAU: To be held in 1960 at British Colonial Hotel and Nassau Beach Lodge:
- Second serendipity conference, January 17-30
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- Postconvention conference, June 18-25
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TEMPLE UNIVERSITY SCHOOL OF MEDICINE, PHILADELPHIA: Postgraduate courses for 1960:
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- Laryngology and laryngeal surgery, April 4-15 and September 26-October 7

For further information, write to: Jackson-Research, Lab 604, Temple University School of Medicine, 3400 North Broad Street, Philadelphia 40.

THE UNIVERSITY OF MICHIGAN MEDICAL CENTER, ANN ARBOR: Postgraduate courses for 1960:

Brief review courses for practicing physicians:
- Gastroenterology, February 22-26
- Rheumatology, March 2-4
- Pulmonary diseases, March 14-16
- Allergy, March 17-19
- Diseases of the heart, March 21-25
- Electrocardiographic diagnosis, March 28-April 2
- Recent advances in therapeutics, April 4-8
- Endocrinology and metabolism, April 11-15
- Clinical neurology, April 18-19
- Pediatrics, obstetrics and gynecology, January 25-29
- Otolaryngology, April 21-23
- Ophthalmology, April 25-27
- Psychiatry, February 29-March 1
- Diagnostic radiology, April 4-6
- Clinical use of radioisotopes, as arranged

Basic sciences and their clinical correlation and application:
- Bacteriology, January 4-16
- Biophysics, January 18-30
- Endocrinology, February 1-13
- Biochemistry, February 15-March 5
- Physiology, March 7-19
- Pharmacology, March 21-26; April 4-9
- Anatomy (obstetrics and gynecology), April 11-30
- Anatomy (surgery), April 11-June 3

For further information, write to: Dr. John M. Sheldon, Director, Department of Postgraduate Medicine, 1610 University Hospital, Ann Arbor.

Radiology FOR PRACTICING PHYSICIANS

Solitary and Multiple Osteocartilaginous Exostoses and Enchondromatoses

PAUL C. HODGES* AND ROBERT D. MOSELEY, JR.

University of Chicago, Chicago

This month's article has been prepared in collaboration with Dr. Robert D. Moseley, Jr., Chairman of the Department of Radiology at the University of Chicago. Dr. Moseley came to the University of Chicago in January 1949 as an assistant resident in radiology, having received his M.D. degree from the Louisiana State University School of Medicine. He was assigned by the University as its representative at the Los Alamos Scientific Laboratory for the year 1950, and subsequently served two years in the United States Navy. He returned to the University of Chicago as an instructor in radiology in July 1954, and in July 1958 he became a professor and chairman of the department.—Paul C. Hodges, M.D.

Solitary Lesions

FOR convenience, solitary osteocartilaginous exostoses usually are classified as benign tumors. They are fairly common, vary widely in size, seldom require surgery, and rarely undergo degeneration into malignant chondrosarcomas. Unlike the multiple variety, their genetic basis is not well established, but morphologically they are indistinguishable from many of the individual lesions of the multiple type. Radiologically, one usually sees a tubular projection of cortical bone springing from the end of the shaft of one of the long bones, such as the lower end of the femur or the upper end of the tibia, and terminating in a bulbous vacuolated cap (figure 1). Almost always the long axis of the exostosis is directed away from the epiphysis. Occasionally, instead of the common pedunculated type, one sees a low, broad-based knob, the so-called sessile type (figure 2a and b). Histologically, the stalk is made up of normal-appearing cortical bone surrounding a small marrow cavity, and the cap shows inclusions of cartilage plus a more or less complete covering mantle of

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cartilage. Particularly when they are deeply covered by protecting muscle, exostoses may go unnoticed until revealed by x-ray examination of the region; more commonly, their presence is known to the patient, and occasionally they interfere with function or become painful following trauma. Most solitary exostoses remain benign throughout the life of the patient, but metamorphosis into chondrosarcoma is not unknown (figure 3); this should be suspected whenever lesions are extremely large or when it can be established that lesions of any size have begun to grow.

In our experience, large exostoses on the ribs are particularly prone to malignant degeneration, but this did not occur in the case illustrated in figure 4.

Solitary enchondromas are cartilaginous masses occurring in the shafts of phalanges, in metacarpal and metatarsal bones, and, less frequently, in the long bones of the upper or lower extremities. Unlike giant-cell tumors, they seldom lie at the articular ends of the bones, but, radiologically, they may be indistinguishable from bone cysts. Frequently, they remain undetected until pathologic fracture occurs and x-ray examination brings them to light (figure 5). Differentiation from cyst is easy in those cases in which the abnormal cartilage has undergone a rather typical splotchy calcification. Malignant degeneration, which is uncommon, has been illustrated in an earlier issue of this Journal.[1]

Multiple Lesions

The work of present-day human geneticists[2] and bone pathologists[3] suggests strongly that exostoses and enchondromas are separate clinical entities rather than variants of one another, but the opposite view prevailed for many years and some of the older writers used the eponym "Ollier's disease" to include both.[4] Others insisted that the term "Ollier" must be limited not only to enchondromatosis but also to instances of unilateral involvement; however, in some of his own publications Ollier did not distinguish sharply between exostoses and enchondromatoses. Ollier's own term "dyschondroplasia"[5] has caused endless confusion, and the vague and now obsolete term "osteogenic disease" reflected European thinking during the time when the two conditions were considered to be one.

Solitary osteocartilaginous exostoses can scarcely be confused with solitary enchondromas and, while most full-blown multiple lesions of the one condition are easily distinguished from those of the other, there are cases in which resemblance is close. Morphologically, solitary lesions of both conditions are practically identical with individual lesions in cases of multiple involvement; however, in both instances there are clinical reasons for considering multiple lesions quite different from solitary ones, and in the cases of exostoses there is genetic ground as well. In both conditions multiple lesions cause deformities, and in both, particularly in multiple enchondromas, there is a tendency toward malignant degeneration.

Multiple Enchondromatosis (Ollier's Disease)

Figure 6 illustrates typical Ollier's disease in both ends of the right femur and tibia in an 18 month old girl. Biopsies are no longer made in such cases, but from earlier workers[6] we know that the abnormal translucent zones in the affected bones represent cartilage. Jaffe says that this cartilage differs from that of solitary enchondromas only by being somewhat more cellular. In spite of much theorizing and a little experimentation,[7] the cause of Ollier's disease remains unknown, but most students agree that it results from a disturbance in the mechanism of bone growth whereby cartilage masses accumulate in a region that should be made up of bone. It is usually said that the condition is not hereditary, but some geneticists believe that it is transmitted as a recessive. The point is important, of course, because if heredity is not involved it is possible that one may find and correct an external factor.

While longitudinal growth is disturbed, it is not stopped; as the affected bone elongates, the cartilage zones elongate as well. Contrary to much of the teaching, unilaterality is not inevitable, but even when both sides are involved, as is illustrated in figure 7, one side usually is more heavily involved than is the

FIGURE 1. Solitary, pedunculated, benign osteocartilaginous exostosis that was confirmed at operation in a 16 year old girl.

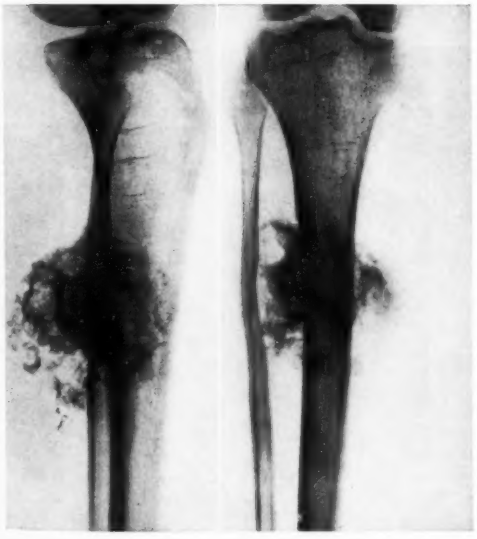

FIGURE 3. Lateral and frontal views of secondary chondrosarcoma developing in solitary osteocartilaginous exostosis of the left tibia in a 24 year old man. Note the mechanical deformation of the fibula.

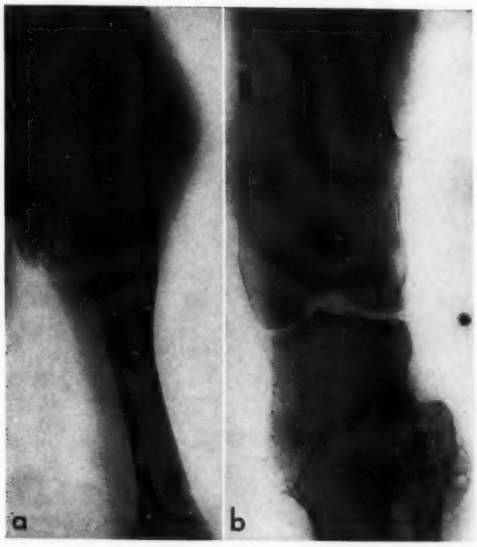

FIGURE 2. Multiple osteocartilaginous exostoses of the mixed pedunculated and sessile type seen in a 23 year old man.

a. At the upper end of the left humerus, the lesions are sessile and resemble enchondromas.

b. Exostoses at the upper end of the right tibia and fibula also are sessile and resemble enchondromas; however, those present at the lower end of the right femur are pedunculated.

There also were lesions in both humeri, knees and ankles.

other. When lesions are limited to the lower extremity there usually is little disability, but involvement of the fingers and hands (figure 8) sometimes causes mechanical interference with function sufficiently severe to require amputation of one or more digits. In adult life, the likelihood of chondrosarcomatous degeneration becomes very great.

It has long been recognized that patients with enchondromas frequently also have soft-tissue hemangiomas, within which there may be phleboliths. When hemangiomas and phleboliths are a prominent feature, the condition sometimes is called Maffucci's syndrome[8] (figure 9).

Multiple Osteocartilaginous Exostoses

This condition, which the British have called "diaphysial aclasis,"[9] is more common

FIGURE 4. Benign osteocartilaginous exostosis at the sternal end of the fourth rib on the left side in a 66 year old man. This condition was found incidentally in chest films and was confirmed at necropsy. Death was not related to this lesion.

FIGURE 5. Solitary benign enchondroma of the proximal phalanx with a pathologic fracture in a 25 year old man.

FIGURE 6. *Left.* Unilateral multiple enchondromas in an 18 month old girl.

FIGURE 7. *Right.* Bilateral multiple enchondromas in a two year old girl. Typical lesions are seen in the femur, tibia and fibula of the right leg. Lesions are present in the tibia and the fibula but not in the femur of the left leg.

than Ollier's disease, less prone to malignant degeneration, and much more definitely established as a hereditary disease that is transmitted as a dominant. Cases of this disease in men outnumber those in women by two to one. The lesions commonly go undetected during early childhood and, while deformities of the forearm may be sufficiently severe to require corrective surgery and larger masses elsewhere in the skeleton may press on nerves or blood vessels or otherwise impair function,

FIGURE 8. Multiple enchondromas of the fingers of the right hand of a four year old girl. Similar lesions were present in the left hand and at the lower end of the right ulna.

FIGURE 9. Severe multiple enchondromas of the left hand in a 56 year old man. Numerous soft-tissue hemangiomas with phleboliths (so-called Maffucci's syndrome) complicated this condition. Secondary chondrosarcoma of the proximal phalanx of the third digit also was present.

There were lesions in the left forearm and the right hand. Forty years earlier, the patient's right leg had been amputated for what was described as a tumor of the tibia at the ankle. A chondrosarcoma eventually developed in the neck of the left femur.

FIGURE 10. Multiple osteocartilaginous exostoses in a 22 year old woman. Lesions were seen in the upper end of the shaft of the right humerus, scapula and ribs.

FIGURE 11a and b. Right and left forearms of the patient described in figure 10. The absence of the lower end of the ulna is a common finding.

FIGURE 13. Same case as figure 10. Lesions are present at the upper ends of both femurs and in the pelvic bones, particularly the right one. Skeletal parts of a 32 week old fetus are seen within the pelvis.

FIGURE 12a. Exostoses of the upper ends and bowing of the lower ends of the tibia and fibula in the patient described in figure 10.
b. Exostoses of both ends of both bones.

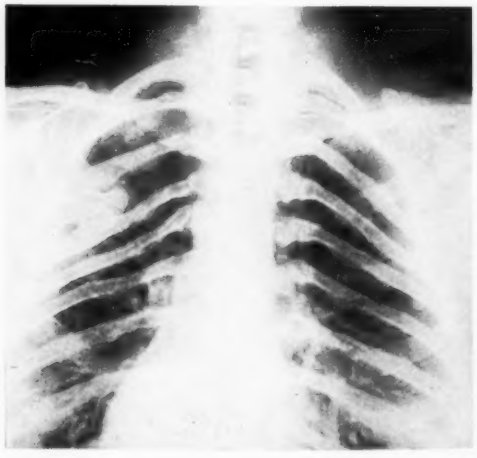

FIGURE 14. Lesions in many of the ribs of the patient described in figure 10. A particularly large lesion is noted in the left scapula.

it is noteworthy that the clinical picture seldom is as alarming as the x-ray examination might lead one to believe.

Figures 10 through 14 illustrate the case of a 22 year old pregnant woman who had dozens of lesions in pectoral and pelvic girdles, ribs and upper and lower extremities. In most of the anatomic sites, frank exostoses could be seen, and there was little reason to confuse the condition with Ollier's disease. In the femur, however (figure 13), the zones of decreased density in the intertrochanteric regions look something like the cartilage zones in Ollier's disease. Comparing this case with that illustrated in figure 6, however, one sees that in Ollier's disease the outline of the cortex is broken wherever a cartilage mass is present at the surface of the bone, whereas in osteocartilaginous exostoses (figure 13) the cortex is continuous.

We have not seen enchondromas and exostoses in the same patient; when they do occur it has been pointed out that the exostoses are small, irregular and not directed away from the epiphysis.

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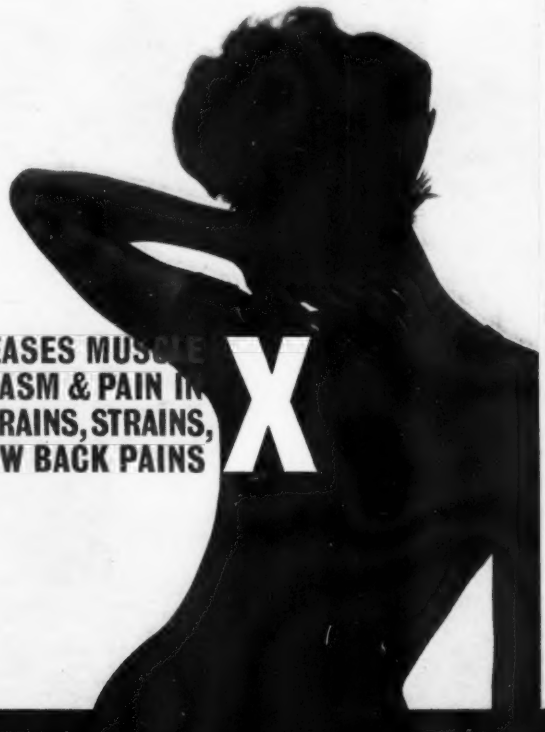

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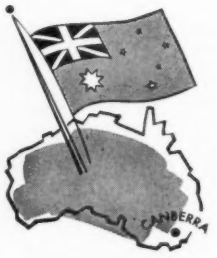

Colposcopy in early detection of carcinoma of the cervix—In the *Medical Journal of Australia*, Dr. Malcolm Coppleson, King George V Memorial Hospital, Sydney, discussed the colposcope and the technic of using this instrument in the diagnosis of carcinoma. The colposcope gives a small-scale stereoscopic magnification 6, 10, 16 or 25 times the actual size of the cervix. It represents a transition from macroscopic to microscopic vision, so that one can see changes in the mucous membrane which are not visible to the naked eye and from which the actual histologic finding may be forecast with surprising accuracy.

Dr. Coppleson described the most common colposcopic findings and the significance of each, pointing out that the colposcope shows that the terms "cervical erosion" and "chronic cervicitis" actually apply to at least eight different conditions. The author defined the relationship between atypical hyperplasia, carcinoma *in situ*, and invasive carcinoma. He told of discovering 11 cases of unsuspected carcinoma of the cervix by colposcopic and cytologic examination, and he stressed the importance of the complementary use of these methods in the detection of preclinical carcinoma of the cervix.

Granulocytic leukemia—In the same journal, Drs. C. K. Hambly and T. I. Robertson reported on a study of 86 patients with chronic granulocytic leukemia who were treated at the Sydney Hospital between 1922 and 1958. The most common symptoms of the disease were anemia, noticeable abdominal swelling, pain and loss of weight. The sex incidence was approximately equal. All age groups were affected, but the peak incidence occurred in persons between the ages of 40 and 60 years.

Patients survived an average of two years from the time the disease was diagnosed; sex, age or the duration of symptoms before diagnosis had little influence on survival time. The survival periods were approximately the same with most forms of treatment, although patients treated with low-voltage x-ray therapy combined with arsenic or benzene died sooner than did other patients in the group. Treatment with MYLERAN® appeared to be at least as effective as was radiotherapy. There was also an indication that those patients who had severe anemia, marked leukocytosis or hepatomegaly at the time that granulocytic leukemia was diagnosed had a poor prognosis; however, the prognosis in such cases is very uncertain.

The disease terminated most commonly with malignant cachexia, acute leukemia or intercurrent infection; hemorrhage remained a particular hazard. Acute terminal leukemia seemed to be part of the natural history of the disease; it was not provoked by any specific form of treatment.

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(Continued on page A-110)

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tial treatment of the grossly enlarged liver or spleen. When resistance to Myleran occurs, other chemicals are of limited usefulness, and radiotherapy may be contraindicated.

AUSTRIA

Interposition of the small intestine after resection of the stomach or rectum for carcinoma—At a meeting of the Viennese Medical Society, Dr. R. Oppolzer discussed the various methods of entero-anastomosis used in cases of carcinoma of the gastrointestinal tract. When resection for carcinoma causes extensive defects in the gastrointestinal canal, intestinal continuity can be re-established (1) by a primary or secondary (two stage) method of direct anastomosis, following extensive mobilization of the two stumps, or (2) by interposing a segment of the small intestine into the defect if the size of the defect makes direct anastomosis impossible. The latter procedure can be done at the first operation. The loop of the small intestine is interposed simultaneously with resection, as formerly was done after total gastrectomy according to the Longmire-Seo method. This procedure has been used successfully in four total gastrectomies done at the Viennese Policlinic. Dr. Oppolzer stated that in the last five years this operation also has been performed without mortality in four cases of extensive resection of the rectosigmoid.

Dr. Oppolzer showed a series of roentgenograms illustrating surgical interposition of the intestine between the esophagus and the duodenum. Fat resorption, splitting of proteins, and fermenting action are brought much closer to physiologic conditions by this method than by operative procedures which do not provide for a duodenal passage. The dumping syndrome and esophageal reflux are eliminated. The loop gradually becomes wider; thus, it acts as a reservoir and substitutes for gastric filling.

Interposition of the small intestine has previously been done only rarely and in those instances always at a second operation. The usual procedure after resection is to perform a colostomy in the transverse colon and to close the lower rectal ampulla as a blind pouch; interposition of the small intestine is done a year later. Scar formation in the lower colon complicates the second operation.

In primary interposition, the small intestine is interposed simultaneously with resection, and passage of stool is temporarily prevented. This procedure extends and prolongs the operation, but it is technically easier than the other method because of the peripheral anastomosis. Closure is done later in a simple operation. Primary interposition is suitable only in selected patients, and it should not be considered when resection of the rectum and sigmoid will take more than about an hour.

Dr. Thurnher stated that roentgenographic follow-ups of gastrectomies done according to the Longmire-Seo method show excellent functional results. The interposed intestinal loop widens somewhat and begins to function as a reservoir. Food does not pass more quickly through the small intestine, and there is no esophageal reflux, even when the patient is recumbent.

Dr. Kyrle described three cases of interposition of the small intestine after total gastrectomy for carcinoma according to the Longmire-Seo method. Five months after this operation was done in a 69 year old man, roentgenograms showed that the intra-abdominal end of the esophagus was somewhat widened; the interposed loop of the small intestine was well filled, and the mucosal pattern was only a little coarser than is the normal pattern. The anastomosis between the interposed loop and the duodenum could not be distinguished, and there was no blockage in the passage. Roentgenograms made three months after this operation in a 56 year old man showed that the anastomosis was functioning normally and that the interposed loop already had formed a type of reservoir. The operation was not successful in the third patient. During the postoperative period, an upper loop of the small intestine was strangulated beneath the mesentery of the interposed intestinal loop, which caused twisting of the mesenteric vessel and necrosis of the loop. Replacement of the loop by a Y-shaped anastomosis was not successful, and the patient died.

In primary interposition, food is better utilized through the formation of a reservoir. There is no tension on the sutures, and biliary reflux, inflammation of the esophagus, and agastric anemia are absent. Dysphagia and strictures from scarring occur less frequently. However, this

(Continued on page A-112)

no asthma symptoms—Prophylactic use of Tedral in any of its 5 convenient dosage forms permits most bronchial asthma patients to breathe normally, live actively, avoid social embarrassment. Tedral keeps patients safely free of constriction, congestion and apprehension. When attacks are frequent, prescribe 1 or 2 plain Tedral tablets q.4.h. plus an additional tablet at the first sign of symptomatic breakthrough. Tedral protects up to 4 hours.

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operation demands a subtle technic, and it places a relatively heavy burden on the patient during the early postoperative period.

Surgical rejuvenation of the joints—To demonstrate an example of surgical rejuvenation of the joints to a meeting of the Society of Physicians in Vienna, Dr. W. Aberle-Horstenegg presented a 68 year old woman who had been hospitalized with advanced arthrosis of both hip joints. Two years previously, the spongioid bony substance in both hips had been removed with a sharp spoon, according to Vogl's method. Following this operation, the patient experienced a noticeable lessening of pain and considerable improvement in the use of her hips. She now can walk for a period of almost three hours, usually without a cane, and has been able to resume her normal household activities. Recently made roentgenograms showed that the articular spaces of the hips had become almost normal in width.

The lecturer recommended use of this relatively minor intervention at other joints. For further improvement in articular mobility, he suggested a preoperative redressement according to Staudinger's method.

Treatment of varicose veins—At the same meeting Dr. R. Gottlob stated that since there are many underlying conditions in varicose veins it is not sufficient to know only one method of treatment.

In Moszkowicz's operation, there is the danger of damaging veins which are located deeper in the legs when the obliterating substance, injected in a retrograde direction, is short-circuited through the larger perforating vessels. Massive thrombosis may develop, or the venous valves may be injured. If only the valves are damaged, insufficiency of the veins, which may last for months, will result. To determine whether or not the obliterating substance will pass into the varices, Dr. Gottlob recommended injecting a solution of 10 ml. of either sodium dehydrocholate or saccharin into the veins before the therapeutic injection. If the patient immediately experiences a bitter taste (from the sodium dehydrocholate) or a sweet taste (from the saccharin), the obliterating substance should not be injected; treatment should be confined to ligation of the veins. If more than 30 seconds elapse before the sensation of taste develops, small amounts of not more than 10 ml. of the obliterating substance may be injected, or ligation of the ectatic perforating veins may be attempted. In addition to this test, all other precautionary measures should be observed in surgery for varicose veins.

ENGLAND

The health of the executive—During a discussion at the Royal Society of Medicine on the contribution of the industrial medical officer to the health of the community, Dr. R. F. Guymer, London, an expert on industrial health, said that the most important single factor which adversely affects the health of the executive is the tempo at which he has to work. This has increased greatly over the last three decades due to the shortening of time and space by improvement in methods of communication and travel. A cable can be dispatched to Australia in the morning and the answer may be on the executive's desk in the afternoon; an executive may attend a meeting in London in the early afternoon and be present at another meeting in New York early the next morning. Other adverse conditions, such as overeating and uncomfortable traveling to and from work, take their toll of his mental and physical fitness.

From experience Dr. Guymer considered that there are four early cardinal signs of an impending breakdown: irritability, indecision, inability to delegate responsibility, and the persistent taking home of work. This state of affairs may first be observed by the industrial medical officer or by the family doctor. As Dr. George Beaumont has stated, "Many a patient who asks for a tonic really requires a sedative." Whichever physician —family doctor or industrial medical officer— first observes these early signs should communicate with the other in order that the appropriate measures may be taken to attempt to preserve the health of the executive and, indeed, of any other worker who shows similar signs and symptoms.

Medical treatment of hypertension—At the annual meeting of the British Medical Association, Professor M. L. Rosenheim, University College Hospital, London, opened the discussion on the medical treatment of hypertension. He discussed his experience with the use of the new drug Darenthin (bretylium tosylate), which specifically blocks sympathetic nerves without in-

(Continued on page A-114)

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hibiting the parasympathetic nervous system. The early trials suggested it was possible to obtain marked postural hypotension with this drug without side effects on the eye or bowel. Dr. J. A. Lewis said there was no doubt that if a 0.5 gm. sodium diet was conscientiously adhered to, a satisfactory drop in diastolic blood pressure could be achieved in many patients. A more promising line of treatment was the combination of ganglion-blocking agents with chlorothiazide or hydrochlorothiazide. Professor W. D. M. Paton said that the effect of adding chlorothiazide to treatment with ganglion-blocking agents was like doing a small venesection.

Lastly, Dr. Lewis discussed the treatment of mild benign hypertension in which there are no symptoms. It is important, he said, to reduce obesity. The sedative effect of phenobarbital is probably preferable to that of reserpine in such patients, in view of the frequency of depression after reserpine. Dr. Jacques Genest, Montreal, stated, however, that reserpine seldom causes depression, provided it is used in small doses (less than 0.5 mg. daily). In relation to hypertension in patients 65 years of age or older in whom the rise in pressure is primarily systolic, it was generally agreed that no treatment is required. In conclusion, Dr. Genest stressed the importance of psychologic factors in the sudden onset of hypertension.

Factors in the breakdown of marriages—At the same meeting of the British Medical Association, Dr. H. V. Dicks, Tavistock Clinic, London, discussed etiologic factors in marital crises. He and his collaborators studied 157 disturbed marriages, which they compared with a control group of happy marriages. The marriage partners they had studied were predominantly of high social status and education; four-fifths owned their own houses and flats. Of 299 spouses, no fewer than 239 came from broken homes or homes with poor parental relations where there was violence between the parents, temporary desertion, and so on. Only 4.2 per cent of the spouses came from emotionally stable homes. In contrast, in the matched control group 54.6 per cent came from good homes. The 299 spouses showed few overt neurotic symptoms, but disturbed parental relations in the home when the spouses were children seemed very important. Under certain conditions the spouses seemed to enact a compulsive repetition of their childhood experience. One of the conditions seemed to be their age. It seemed that marriages came to a crisis when the partners reached 35 or so, when the children were off to school. Dr. Dicks thought this midterm crisis might be partly physiologic (hormonal aging) or partly the consequence of middle-class people becoming isolated within the family group and demanding more of marriage and family than they could give.

Abdominoperineal resection: why leave the perineal wound open?—It has been customary in general surgery to believe that a large cavity left in the body after a major resection requires drainage. This is untrue, provided that hemostasis is complete and that there is no mucus-secreting or actively discharging source of infection into the cavity. If serum accumulates, as it often does, it can be left alone unless it bulges the perineum unduly, when it can be aspirated. In pneumonectomy, even when the lung has been full of pus and when it has already perforated and formed an empyema, the chest can be safely closed without drainage, again provided that the bronchus is completely closed and covered with a living graft, that hemostasis is assured and that any empyema present is excised.

At a discussion in the section of proctology at the Royal Society of Medicine, Mr. Donald Barlow, London, remarked that those who care for patients who have had abdominoperineal resection of the rectum cannot fail to be touched by the pain experienced by patients who undergo repeated packings and dressings of a large perineal wound. Primary closure of the perineum is a practical proposition in the majority of cases. Experience in both thoracic and general surgery allows the principles of the one to be applied with advantage to the other.

Some years ago, these reflections led Mr. Barlow to wonder whether the perineal wound could not be closed with safety after abdominoperineal resection. Because of the difficulty in keeping a satisfactory perineal dressing in position, sepsis and even secondary hemorrhage occurred frequently. Urinary difficulties, the need for prolonged catheterization, and later urinary sepsis were matters of moment.

Mr. Barlow first closed a perineal wound completely some six years ago. Earlier he had closed the perineum but used a closed drain with slight suction. This was soon abandoned, as it was in the case of pneumonectomy, because of risk of sepsis and because the drain was unnecessary. After radical surgery the levatores ani have large-

(Continued on page A-116)

When the emotional component of premenstrual tension becomes severe enough to interfere with normal activities and relationships, PROZINE is usually advantageous. It is designed for the treatment of moderate to severe emotional disturbances, either alone or complicated by organic symptoms.

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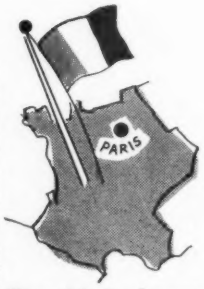
ly gone, but there is plenty of fatty tissue and skin to bring together in a good, thick wound closure.

Routine closure is now used by Mr. Barlow except in rare cases in which special contraindications apply. Average convalescence is two to two and a half weeks. If complete closure is more widely adopted, resection of the rectosigmoid will lose its sinister reputation and patients will be able to go home in as short a time as they would after a simple laparotomy. As with complete closure after pneumonectomy, sterile fluid may persist for a while within the lower pelvis. Urinary troubles are minimized and normal urinary flow is established after 24 to 48 hours.

FRANCE



Adenoma of the prostate—Several important works on the pathogenesis of prostatic adenoma have been published in Europe in recent years. Gil Vernet demonstrated that adenoma of the prostate is the result of insufficient secretion of a hormone by the prostate. That this inadequate secretion is probably due to some hereditary cause is proved by the fact that uterine fibromas, the homologue of prostatic adenoma, have been found in the forebears of persons who have prostatic adenoma.

Van Euler and Bergstrom isolated the prostaglandin of the ram, a substance related to acetylcholine and possessing vasodilative properties. Prostaglandin contracts the fibers of smooth muscles, provokes lasting arterial hypotension after briefly elevating the blood pressure, and inhibits the production of spermatozoa, although such inhibition is quickly reversible. In time, it changes the seminal vesicles and causes the formation of adenomas in the prostate.

Professor Thiéblot and co-workers of Clermont-Ferrand studied the pathogenic effect of extracts prepared from adenomas of the prostate. They prepared an aqueous extract of the adenoma which was free of proteins and lipids. Effects obtained with extracts from both prostatic adenomas and uterine fibromas were similar, but effects obtained with extract from smooth muscle fibers were not comparable.

Extract from prostatic adenoma differs from prostaglandin, which is an oily solution or suspension of a nitrogen-free methyl ester of which the maximal absorption corresponds to 2800 Å in the ultraviolet portion of the spectrum. In contrast, the adenoma extract is an aqueous solution; it has a neutral reaction and is rich in trace minerals such as iron, zinc, magnesium, manganese, copper, calcium and silver. It is a mixture of glycoproteins, rich in mucoid substances and devoid of any enzymatic activity. It does not cause contraction of smooth muscle fibers, and due to the discharge of epinephrine it raises rather than lowers the blood pressure.

The authors' studies showed that repeated injections of the extract into three week old, sexually immature rats inhibited the development of the genital tract. Growth was blocked at the spermatogonial stage, and an adenoma developed in the prostate. In eight week old, sexually mature rats genital development retrogressed following injection of the extract, and the spermatozoa disappeared. These lesions were reversible in six to eight weeks.

Lesions in the testes of rats treated with the extract seemed to be comparable to the reversible lesions seen in the testes of men with prostatic adenomas. Aspiration biopsies of the testes have shown that such lesions, even in people of advanced age, will retrogress within one or two years after removal of the adenoma and that there will be no further change except that which is related to aging.

Professor Thiéblot and co-workers concluded that the secretory activity of adenomas provokes an intoxication which is reversible but which complicates the disturbing effect of functional retention of urine in the bladder.

Treatment of infantile convulsions with pyridoxine—From 1951 to 1953 in the United States, reports appeared of convulsions which occurred in infants as a result of vitamin B_6 deficiency which was caused by the exclusive use of wholly devitaminized dry milk. More recently, cases of newborn babies affected by convulsive attacks which responded to vitamin B_6 therapy have been reported in the American literature.

Professor Julien Marie and co-workers described the successful use of vitamin B_6 therapy in a baby who had had recurrent convulsive attacks since the age of 15 days. The attacks were not controlled by barbiturates or by other neurologic sedatives; however, they were stopped immediately by an injection of pyridoxine. This injection was effective for five days; further con-

vulsions were successfully controlled by an injection of 100 mg. pyridoxine.

Between attacks the infant seemed to be restless and moved spasmodically on the least auditory or motor stimulation. The encephalogram was disordered, but it became normal immediately after an injection of pyridoxine. The child exhibited abrupt movements of the eyes of the type termed "rolling eyes" in the American literature.

Complete protection from convulsions was obtained by daily oral administration of 4 mg. pyridoxine, which was the minimal effective dosage. When pyridoxine was injected at five day intervals, the infant showed only slight improvement in development. However, when the vitamin was administered daily, the infant's weight increase was normal, in spite of the gross psychomotor retardation present.

The pathogenesis of such convulsions is obscure. The disorder is acquired rather than congenital and seems related to the metabolism of pyridoxine in the brain. This would suggest that pyridoxine should be used to treat convulsions in infants who do not respond to the usual antiepileptic drugs.

These reports appeared in *La semaine des hôpitaux de Paris.*

GREECE

Amebic colitis—Studies at the National University of Athens School of Medicine showed that only 60 of 3000 patients with colitis (often diagnosed as amebic colitis) actually had *Endamoeba histolytica* in their stools. These patients came from all parts of Greece. This low carrier rate, especially among patients with colitis, is apparently representative in Greece. Entobex, a new phenanthroline-quinone derivative, proved to be effective and well tolerated in 30 cases of amebic colitis.

The results of these studies were published in the *Journal of Tropical Medicine and Hygiene.*

Bacterial resistance to chemotherapy—In the *A.M.A. Archives of Internal Medicine,* G. K. Daikos and M. Athanasiaou reported on a series of 615 cases of gram-negative infections. They found that 197 (31.5 per cent) of the cases were caused by bacteria resistant to the commonly used chemotherapeutic preparations. Twenty of these 197 patients died. Sensitivity was tested against penicillin, novobiocin, nitrofurantoin, streptomycin, oxytetracycline, tetracycline, chloramphenicol, oleandomycin and sulfamethoxypyridazine. *Pseudomonas aeruginosa* was the most resistant of all bacteria (83.7 per cent), followed by *Proteus* (44.6 per cent), *Klebsiella pneumoniae* (24 per cent), and *Escherichia coli* (17.4 per cent).

The sensitivity of gram-negative enteric bacilli to higher concentrations of penicillin (30 and 60 μg. per milliliter) also was tested. Of 250 strains of bacteria, 72 proved sensitive to 60 μg. penicillin per milliliter. Penicillin proved effective in selected cases of urinary tract infections which were found to be resistant to other antibiotics that were used.

Strains of *Staphylococcus* tested at this time for sensitivity to antibiotics were found to be more resistant than they were when tested in 1956 at the same hospital. Of all strains isolated, 89 per cent were resistant to penicillin; novobiocin and erythromycin in low concentrations proved the most effective against these strains. It was found that staphylococcal infections do not occur as frequently in Greece as in the United States and other countries.

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turbances seen daily in the clinics or by the general practitioner."*

Rheumatic Pneumonia in Children

DAVID GOLDRING, M. R. BEHRER, W. THOMAS, G. ELLIOTT AND G. BROWN*

Washington University School of Medicine, St. Louis

The pathogenesis of rheumatic pneumonia is not known. It seems likely, however, that the inflammatory process damages the capillary walls and permits exudation of fibrin into the alveoli.

Rheumatic pneumonia reduces the chances of survival in cases of rheumatic fever. Patients who do survive have severe heart disease.

Hormonal therapy may increase the chance of survival and possibly reduce the severity of residual heart disease.

RHEUMATIC pneumonia has been the subject of many studies. The first report of a study of this disease was published in 1788.[1] The existence, cause and frequency of this pulmonary manifestation of rheumatic fever have long been controversial issues.[2] There is disagreement about the frequency with which rheumatic pneumonia is seen, and there are many hypotheses about its pathogenesis.

DAVID GOLDRING

We believe that the diagnosis of rheumatic pneumonia can be made post mortem, since it produces a pulmonary reaction that is distinctive but not pathognomonic. This reaction can easily be recognized by microscopic examination of sections of the affected organ. We also believe that the clinical picture is quite striking and that rheumatic pneumonia can be recognized ante mortem.

*Departments of Pediatrics, Pathology and Radiology, Washington University School of Medicine and the St. Louis Children's Hospital, St. Louis, Missouri.

Incidence

This manifestation is not rare in our experience, since we recently reported 23 cases in which the patients were observed at the St. Louis Children's Hospital in a period of eight years.[3] In 16 of the cases, the patients died, and the diagnosis of severe rheumatic fever and rheumatic pneumonia was verified at necropsy. In the seven cases in which the patients survived, the clinical course of the disease was strikingly similar to that in the cases in which the patients died. We, therefore, be-

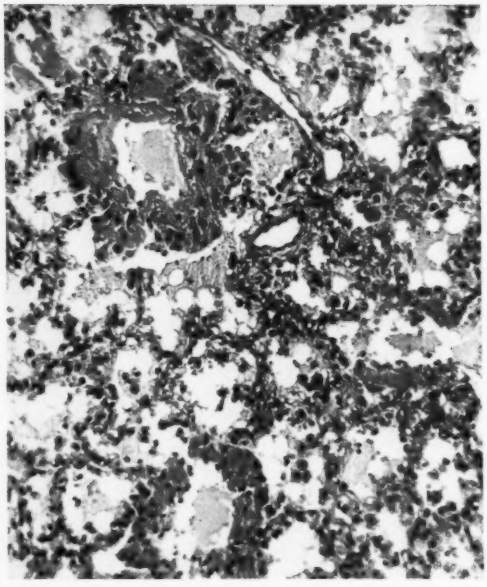


FIGURE 1. Photomicrograph of section of lung showing edema and congestion. Some of the alveolar spaces are filled with edema fluid. In other areas, fibrinous material is packed against the walls of the alveoli. The inflammatory cells are chiefly mononuclear cells. (Hematoxylin-eosin stain; x 150.)

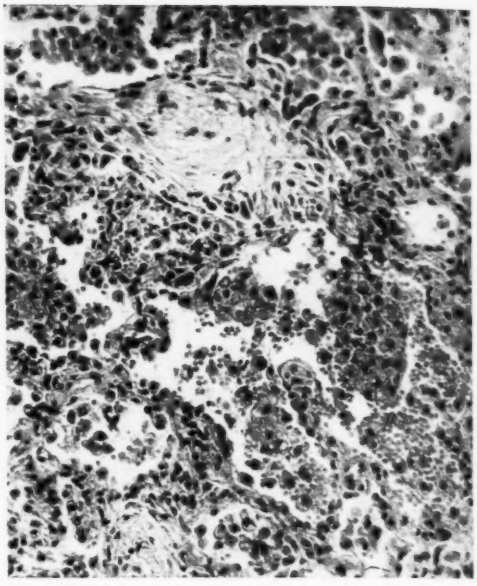


FIGURE 2. Photomicrograph of section of lung. Many of the alveolar spaces are filled with fibroblasts and the walls of the alveoli are difficult to identify. There also are areas of hemorrhage, edema and mononuclear cell infiltration. (Hematoxylin-eosin stain; x 150.)

(All illustrations reproduced from: Goldring, D., Behrer, M. R., Brown, G. and Elliott, G.: Rheumatic pneumonitis: Report on the clinical and laboratory findings in twenty-three patients. J. Pediat. 53:547 [November] 1958.)

lieve that the diagnosis of rheumatic pneumonia was justified in these seven cases.

Scott, Thomas and Kissane[4] recently reported that they were able to demonstrate the presence of some lesions of rheumatic pneumonitis in 54 (62 per cent) of 87 cases in which children died of rheumatic fever at the St. Louis Children's Hospital and the Barnes Hospital between 1919 and 1954. Aschoff bodies or typical veruccae were present in the heart in all of the cases. Sections of the lungs were examined microscopically especially for fibrinous exudate in the alveolar sacs or respiratory ducts, hyaline membrane, necrosis of the alveolar walls and thrombi. The pathologic changes were graded as slight if less than 10 per cent of the tissue available for microscopic examination was estimated to be involved, as moderate if from 10 to 20 per cent of the available material was involved, and as advanced if more than 20 per cent of the available material was involved. On the basis of these criteria, the pathologic changes were graded as slight in 21 (39 per cent) of the 54 cases, as moderate in 29 cases (54 per cent), and as advanced in 4 cases (7 per cent).

Pathology

The pathogenesis of this pulmonary manifestation of rheumatic fever is not understood. As described by Scott, Thomas and Kissane,[4] the pathologic picture suggests capillary injury and subsequent seepage of fibrin into the alveoli. Microscopic examination may reveal a fibrin ball in an alveolus and an associated infiltration with mononuclear cells. On the other hand, the fibrin may be whipped about the alveolar surface by respiratory efforts so as to form an asphyxial membrane which would prevent proper exchange of gases (figure 1).

The pneumonitis may progress and rather marked fibroelastic proliferation may occur in the fibrin matrix in the alveolus (figure 2). When these changes are observed post mortem in a case in which the clinical picture was typical of rheumatic myocarditis, they help to establish the diagnosis of rheumatic pneumonia. Although these changes are not pathognomonic, they certainly can be distinguished from the pulmonary reactions caused by pulmonary edema, congestive heart-failure and superimposed bacterial infection, all of which may occur concomitantly with rheumatic fever.

Diagnosis

We believe that the clinical picture of rheumatic pneumonitis is distinctive and that the diagnosis can be made ante mortem. There are, however, a number of diseases that must be considered when the differential diagnosis is made.

The presence of bacterial pneumonitis can be ruled out by the persistent and migrating character of the pulmonary infiltration as disclosed by roentgenographic examination. In our seven cases in which the patients survived, the development of bacterial pneumonitis would be unlikely because penicillin was administered parenterally, and streptomycin and ACHROMYCIN® also were administered when the patients were treated with cortisone or METICORTEN®. Although necropsy revealed evidence of bacterial pneumonitis in 7 of the 16 cases in which the patients died, this lesion was considered minimal and unimportant as a contributing cause of death.

The presence of viral pneumonia cannot be excluded absolutely, but this is a rare complication of acute rheumatic fever. Necropsy did not suggest the presence of this complication in any of the 16 cases.

Rheumatic pneumonitis may be impossible to distinguish from the pulmonary changes produced by congestive heart-failure, severe myocarditis or pulmonary edema. The persistent and migrating character of the pulmonary infiltration and the absence of the usual findings associated with congestive heart-failure will be of assistance in making the differential diagnosis.

Symptoms and Signs

The child with rheumatic pneumonia appears desperately ill and obtunded. His eyes have an anxious appearance, and there is flaring of the alae nasi. All of his efforts are being used to obtain sufficient air. The tachypnea is especially striking, and the respiratory rate at times may be as rapid as 100 per minute. The breathing is often grunting in type. The child is pale, and inspection of the lips and nail beds may reveal a slight cyanotic tinge. A persistent, dry, hacking cough may be present.

Examination of the heart reveals severe pancarditis. The heart is enlarged, the cardiac sounds are distant and mushy, and the cardiac rate is rapid. Systolic and diastolic murmurs may be heard both at the apex and at the right side of the base. Careful physical examination of the chest is not possible because of the critical condition of the patient. Physical examination of the lungs usually discloses few signs, and there often is a poor correlation between the results of auscultation and the roentgenographic and pathologic findings.

Roentgenographic examination revealed pulmonary infiltration in 10 of the 16 cases in which the patients died. In nine of these 10 cases, it also revealed marked generalized enlargement of the heart. This examination disclosed pulmonary infiltration in all of the seven cases in which the patients survived, and it also revealed cardiac enlargement in six of these seven cases. In all of the six cases, the cardiac enlargement persisted after the patients recovered from rheumatic pneumonia.

Pulmonary infiltration appeared and disappeared rapidly, and it was migratory in many cases. In seven cases, a homogeneous zonal infiltration variously involved the inner, middle and upper thirds of the pulmonary fields. This infiltration usually was bilateral, and it usually was characterized by a clear zone about the hili. In two cases, there was a segmental or lobar infiltration that suggested organization or infarction, and both of these types of infiltration occurred in one case.

In most of the cases, electrocardiography revealed abnormal findings compatible with

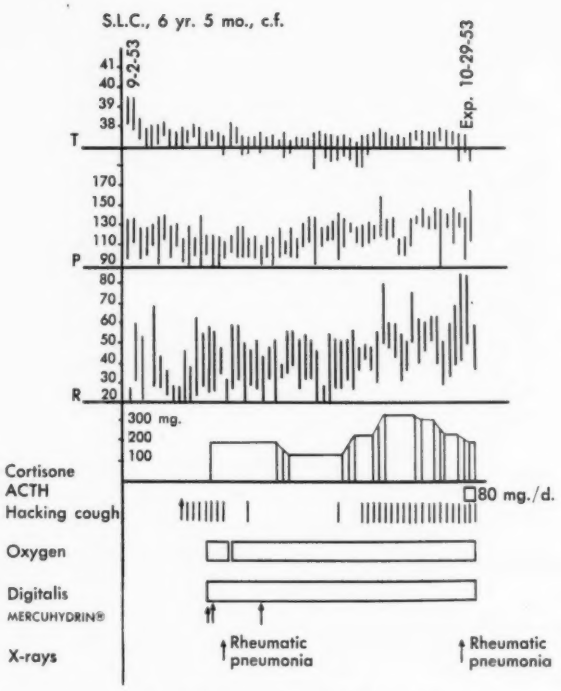


FIGURE 3. Clinical course of the disease in case 1.

myocarditis. These findings included tachycardia, prolongation of the A-V conduction time, and depression or inversion of the T wave. Moderate pyrexia, anemia and leukocytosis occurred in most of the cases. The value for the hemoglobin was less than 10 gm. per 100 ml. of blood, and the leukocyte count was higher than 12,000 per cubic millimeter.

Case Reports

We shall report two cases in order to illustrate the clinical course of rheumatic pneumonia. In case 1, the patient died after the disease had been present for two months. The diagnosis of rheumatic pneumonia was proved by necropsy. In case 2, the patient survived an attack of rheumatic pneumonia which lasted for three months. Since the clinical course of the disease in this case was strikingly similar to that of the disease in case 1, we believed that a diagnosis of rheumatic pneumonia was justified.

Case 1—The clinical course of the disease in this case is illustrated in figure 3. Initially, there was a brief febrile episode. Tachycardia was present when the patient was admitted to the hospital, and it persisted until she died. The most striking feature was tachypnea. At times, the respiratory rate became as rapid as 80 per minute. A cough persisted during the entire course of the disease. Total doses of 10 mg. of cortisone per kilogram of body weight and 0.14 gm. of salicylates per kilogram of body weight were administered. Since the liver was not enlarged and there was no evidence of edema, we were not certain that congestive heart-failure was present. However, the patient was digitalized by the administration of a total dose of 0.033 mg. of digitoxin per kilogram of body weight. Subsequently, a maintenance dose of 0.0033 mg. per kilogram of body weight was administered daily. During the first two weeks that the patient was in the hospital, penicillin and streptomycin were administered parenterally. At the end of that period, the administration of streptomycin was discontinued and the administration of Achromycin was started.

Serial roentgenograms (figure 4) demonstrated the relentless course of the disease. Ten days after the patient was admitted to the hospital, a roentgenogram (figure 4a) revealed cardiomegaly but no evidence of pulmonary infiltration. Eight days later, a roentgenogram (figure 4b) revealed moderately extensive pneumonia which was most marked in the upper part of the right lung. Thirty-two days after the patient was admitted to the hospital, a roentgenogram (figure 4c) clearly showed the zonal character of the pulmonary infiltration of the outer third of the right lung. A clear zone was evident in the perihilar area. The extent of the pneumonia appeared to have decreased in the left lung, but it was apparent that the cardiac enlargement had progressed. Twelve days later (three days before the patient died), a roentgenogram (figure 4d) revealed that the extent of the pneumonia in the right lung had decreased but that infiltration had recurred in the left lung. The heart had continued to enlarge.

Necropsy disclosed pancarditis and an occasional Aschoff body, hypertrophy and dilata-

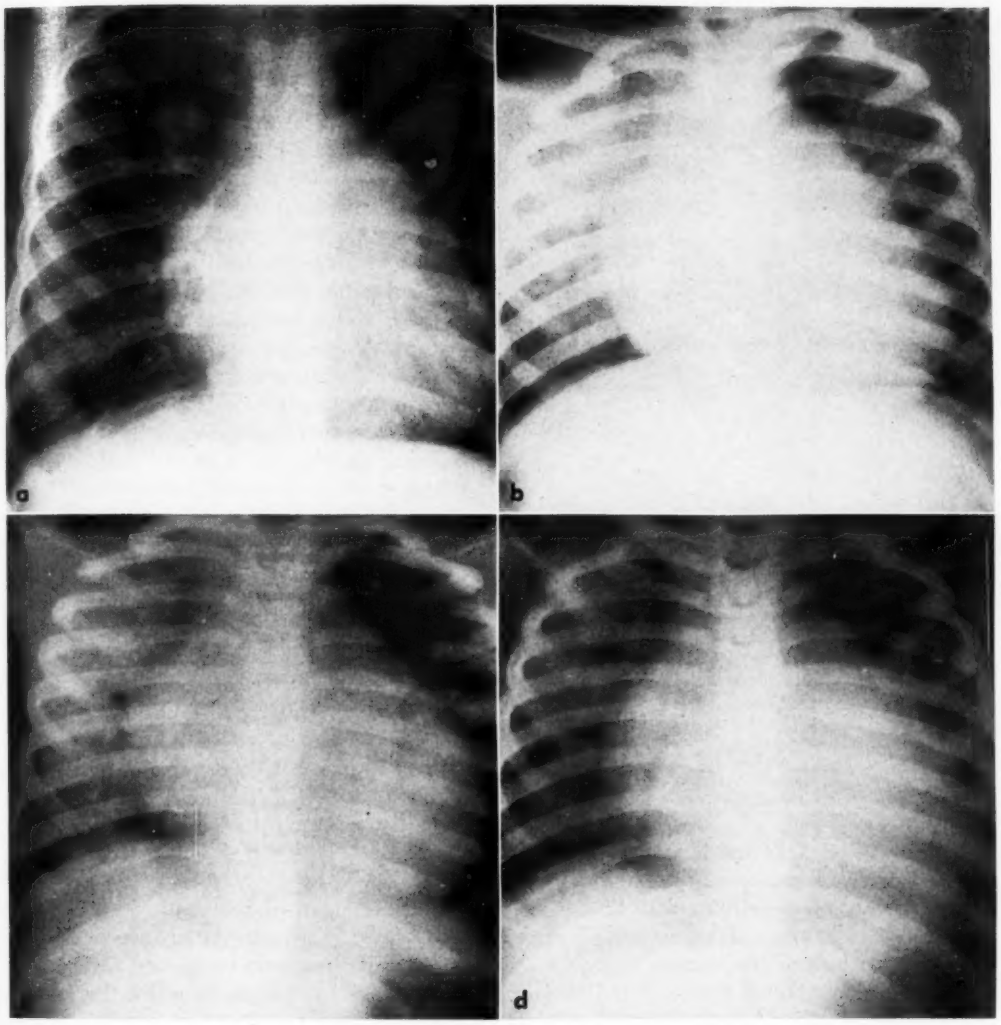


FIGURE 4. Roentgenograms of the chest in case 1.
a. Roentgenogram made 10 days after the patient was admitted to the hospital. It shows cardiomegaly but no evidence of pulmonary infiltration.
b. Roentgenogram made 18 days after the patient was admitted to the hospital. It shows infiltration of the entire right lung and a portion of the upper part of the left lung. The heart appears larger than it was previously.
c. Roentgenogram made 32 days after the patient was admitted to the hospital. It clearly demonstrates the zonal character of the infiltration of the outer third of the right lung. A clear space can be seen in the perihilar area. The pneumonia in the left lung has practically disappeared, but the heart has continued to enlarge.
d. Roentgenogram made 12 days after the one shown in (c), and three days before death. It shows some clearing of the infiltration of the right lung but more definite involvement of the left lung. The size of the heart has continued to increase.

tion of the heart (the heart weighed 180 gm.), and hydropericardium (the pericardial sac contained 50 cc. of fluid). Both lungs were mottled, dark reddish brown in color, and the lobular architecture was somewhat indistinct. Advanced organizing pneumonitis was present

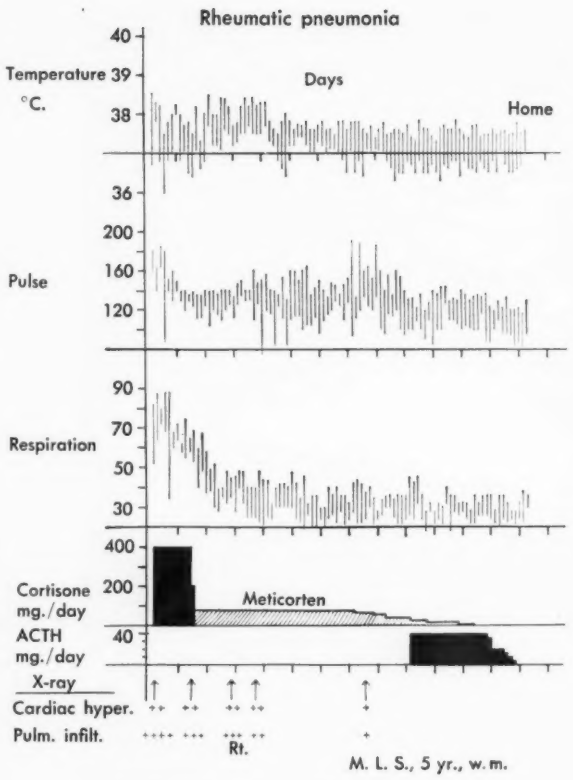


FIGURE 5. Clinical course of the disease in case 2.

in all of the lobes of the lungs. Microscopic examination of a section of the lung revealed that many alveoli were filled with fibroblasts. There also were areas of hemorrhage, edema and mononuclear cell infiltration (figure 2).

Case 2—The clinical course of the disease in this case (figure 5) was similar to that in case 1. We, therefore, believed that a diagnosis of rheumatic pneumonia was justified. The symptoms included fever, tachycardia and striking tachypnea. The patient was treated in the same manner as the patient in case 1, except that the dose of the hormone was somewhat larger, that is, 15 mg. per kilogram of body weight per day. During the first two or three days of the illness, the patient probably had episodes of pulmonary edema, severe myocarditis, congestive heart-failure and rheumatic pneumonitis.

During the second week of the illness, the dominant clinical picture apparently was that of rheumatic pneumonitis. The liver, which seemed to be enlarged during the first week of the illness, became smaller, and there was no evidence of edema or oliguria. Our impression that the patient had rheumatic pneumonia was justified by the roentgenographic findings. Serial roentgenograms (figure 6) demonstrated a variable pattern of pulmonary infiltration which lasted for two months.

On the day that the patient was admitted to the hospital, a roentgenogram of the chest (figure 6a) revealed marked cardiomegaly and extensive pneumonia. The pulmonary infiltration on the right side appeared segmental, which suggested pulmonary infarction or organizing pneumonia. The infiltration of the left lung was more zonal in character. On the nineteenth day that the patient was in the hospital, a roentgenogram (figure 6b) revealed that the pneumonia had become more diffuse and involved the inner and middle zones of both lungs. Only four days later, a roentgenogram (figure 6c) revealed marked resolution of the pneumonia. Two months after the patient was admitted to the hospital, a roentgenogram (figure 6d) revealed that the pulmonary infiltration had cleared completely. Marked cardiac enlargement and chronic pulmonary congestion persisted.

Prognosis

The prognosis of rheumatic pneumonia is very grave. It reduces the chance of survival in cases of rheumatic fever, and severe heart disease persists in cases in which the patients survive the rheumatic pneumonia.

Treatment

Cortisone was administered in seven of the 16 cases in which the patients died (figure 7), and cortisone or Meticorten was administered in five of the seven cases in which the patients survived (figure 8). As can be noted in figures 7 and 8, the doses of cortisone that were administered to the seven patients who died were variable and were uniformly smaller than the doses of cortisone or Meticorten that were administered to the five patients who survived. The seven patients who were treated with cor-

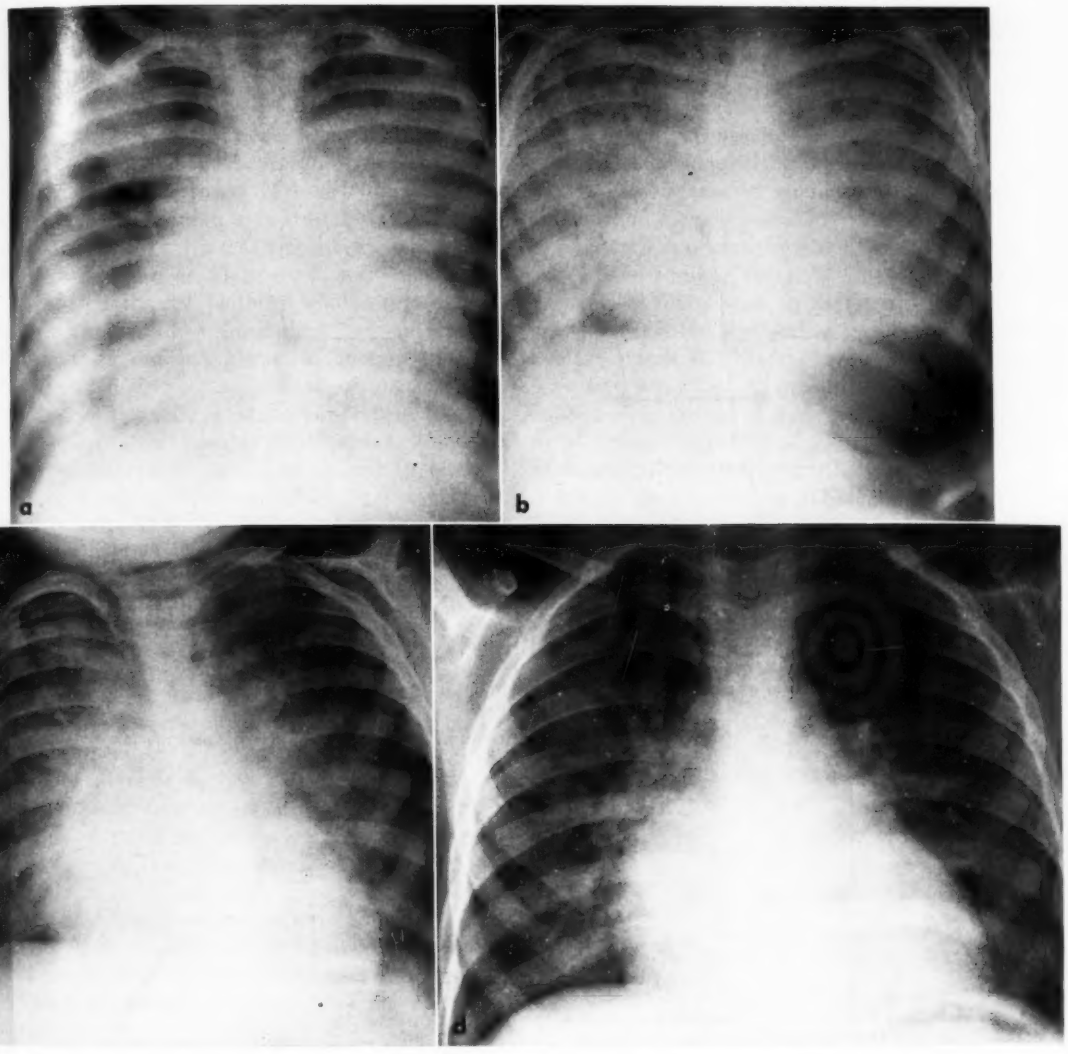


FIGURE 6. Roentgenograms of the chest in case 2.
a. Roentgenogram made when the patient was admitted to the hospital. It shows marked cardiomegaly and extensive pneumonia. The pulmonary infiltration is segmental in the right lung and zonal in the left lung.
b. Roentgenogram made 19 days after the patient was admitted to the hospital. The infiltration has become more diffuse and has involved the middle and inner zones of both lungs. The heart has continued to enlarge.
c. Roentgenogram made 23 days after the patient was admitted to the hospital. It shows marked resolution of the infiltration, but the heart has continued to enlarge.
d. Roentgenogram made two months after the patient was admitted to the hospital. It shows residual cardiomegaly and pulmonary congestion, but there is no evidence of pneumonia.

tisone and died were among the first patients that we treated with this hormone after its introduction, and the smaller doses represent the doses that were being recommended at that time. The five patients who were treated with cortisone or Meticorten and who survived were observed in the past two years, and the doses administered to these patients represent the

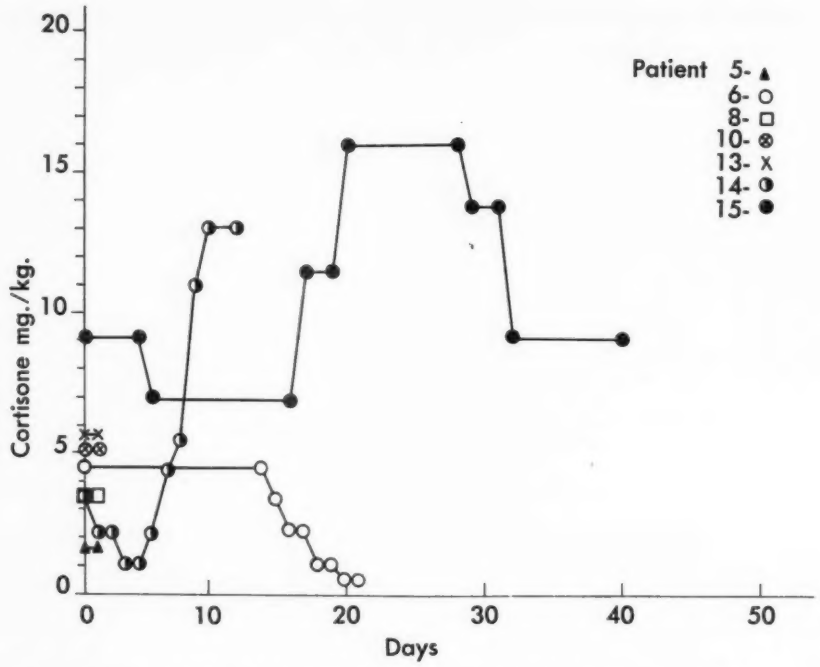
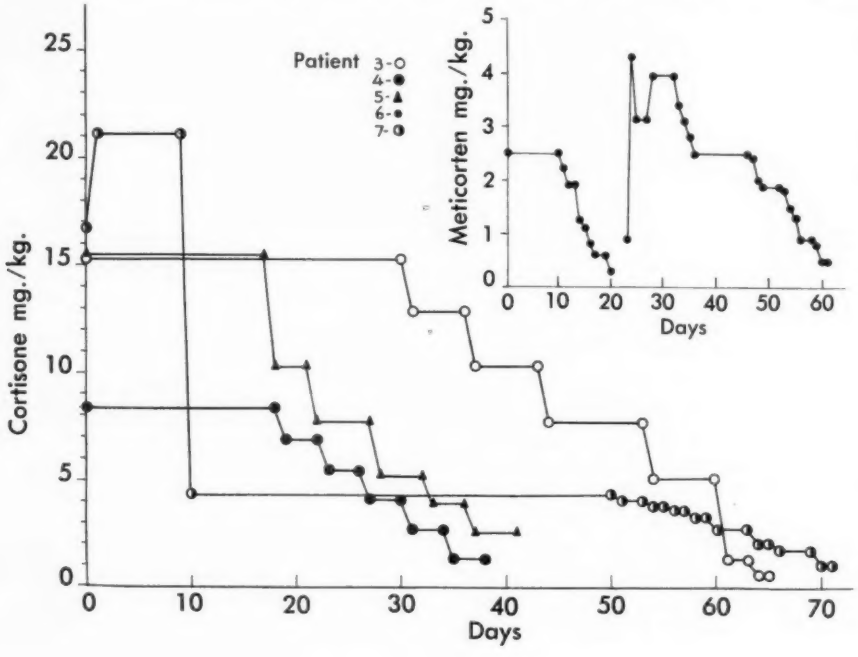


FIGURE 7. Doses of cortisone administered in seven of the 16 cases in which the patients died.

FIGURE 8. Doses of cortisone or Meticorten administered in five of the seven cases in which the patients survived.



trend toward the administration of larger doses of these hormones.

Results

Since the number of cases used in our study is small, our conclusions regarding the effectiveness of cortisone or Meticorten are speculative. Briefly stated, our results were as follows. Of the 11 patients who were not treated with cortisone or Meticorten, only two survived. Of the 12 patients who were treated with one of these hormones, five survived. This suggests that hormonal therapy possibly may increase the chance of survival in cases of rheumatic pneumonia. In four of the five cases in which the patients were treated with cortisone or Meticorten and survived, roentgenographic examination disclosed cardiomegaly. Mitral insufficiency was present in all of the five cases, and aortic insufficiency was present in two of the cases. In the two cases in which the patients were not treated with cortisone or Meticorten but survived, roentgenographic examination disclosed cardiomegaly, and there was clinical evidence of mitral and aortic insufficiency. This suggests that hormonal therapy possibly decreases the degree of residual heart disease. In view of our experience and that of other authors,[5] the value of hormonal therapy in cases of rheumatic fever is still unsettled. Although the effectiveness of cortisone and Meticorten has not been dramatic in our experience, we believe that these hormones should be used in the treatment of any child who has severe rheumatic fever.

Summary

The pathogenesis of rheumatic pneumonia is not understood. It seems likely, however, that damage of the capillary walls by the inflammatory process alters the permeability of these vessels and permits the exudation of fibrin into the alveoli. The fibrinous pneumonitis results from the same capillary changes that produce the fibrinous exudate in the joints, pericardium and other structures.

Rheumatic pneumonia can be diagnosed post mortem by microscopic examination of sections of the lungs. It also can be diagnosed during life because it produces a distinctive clinical and roentgenographic picture.

Rheumatic pneumonia is not a rare complication of rheumatic fever. We have observed 23 cases of this disease at the St. Louis Children's Hospital in a period of eight years, and Scott, Thomas and Kissane[4] recently reported that they were able to demonstrate the presence of some lesions of rheumatic pneumonitis in 54 (62 per cent) of 87 children who died of rheumatic fever between 1919 and 1954.

Rheumatic pneumonia is associated with a severe form of rheumatic fever. It reduces the chance of survival in cases of rheumatic fever, and severe residual heart disease persists in cases in which the patients do survive. Hormonal therapy may increase the chance of survival, and possibly may reduce the degree of residual heart disease in cases in which the patients survive.

We wish to thank Dr. P. J. White for his helpful criticism in the preparation of this paper.

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The Developing Philosophy of Surgery of Cancer of the Colon

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A survey of surgeons representing a cross section of the country showed divergent opinions regarding the treatment of choice in a case in which exploration was negative after a patient had sloughed polyps of grade 1 adenocarcinoma.

The current trend toward treating cancer of the colon or rectum by extensive removal of mesenteric vascular-lymphatic node-bearing tissue is opposed by those who fear this method will lead to premature experimental and radical surgery.

The therapeutic approach to this disease must be predicated on the accumulated collective experience with the pattern of each type of cancer.

RALPH M. MUGRAGE

THE following questionnaire and case history were sent to 50 surgeons comprising a geographic and academic cross section of the country. The purpose of this paper is to report on the 35 answers and comments received and to present a general discussion regarding the problem of cancer of the colon.

Questionnaire and Information Sent to Surgeons

Dear Doctor:

Enclosed is a case history of a patient posing an interesting and serious problem from a surgical judgment standpoint.

There are, as you can see, some important unknowns in the case, namely, the site of the sloughed adenocarcinomatous polyps of the colon and the extent of invasion in the wall of the colon. The patient was operated on by laparotomy, and there were divided opinions as to the procedure to follow after negative exploration.

The problem of this case is being presented to some 50 surgeons throughout the country, and I would greatly appreciate your interest

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The opinions or assertions contained in this discussion are the private ones of the author and correspondents and are not to be construed as reflecting the views of the Navy Department or the Naval service.

in checking the procedure you would follow, with any comments you care to make. It is my intention to incorporate this information in a surgical publication.

Case history—The patient is a 49 year old housewife who, in the early morning of April 3, 1956, had a sudden urge to stool and passed a red liquid "bloody" stool without feces, appearing to be about 1 pt. in volume and causing her to feel weak, dizzy and faint. During the same day, she had two more bloody stools, darker red and lesser in amount, and recovered from the last bloody stool two globular masses of tissue, which she put in a small bottle of rubbing alcohol and brought with her to the hospital on April 6, 1956, when she was admitted.

The patient had had no vomiting, and stools returned to normal color the day after onset of melena.

The patient's history included a diagnosis of duodenal ulcer and gastric ulcer in December 1954; after three weeks of intensive therapy, x-ray showed the gastric ulcer had healed. Physical examination was within normal limits, with the exception of moderate generalized abdominal tenderness. Laboratory studies on admission showed a white blood cell count of 6200 with 52 neutrophils, 46 lymphocytes and 2 monocytes; hemoglobin was 14.5 gm. and hematocrit 42. Urinalysis was negative.

The pathologic report on the tissue passed with hemorrhage was as follows: Gross: Specimen consists of two rounded polypoid masses, firm and grayish-white in color. Four sections were taken. Microscopic: Sections show fragments of polypoid, well-differentiated adenocarcinoma with no pedicle and consisting of neoplastic colonic mucosa dispersed around a central core of fibrous tissue and muscularis mucosae infiltrated by tumor. Diagnosis: grade 1 adenocarcinoma of the colon.

Two preoperative sigmoidoscopic examinations to the level of 25 cm. were negative. One barium enema with air contrast study was negative, and a repeat barium enema with air contrast study two days later suggested two radiolucent areas in the distal end of the transverse colon, which were interpreted as most likely representing polyps.

On April 20, 1956, exploratory laparotomy was performed;* in a thorough exploration, including inspection of the lumen of the colon from the cecum to the lower sigmoid through two colotomies, no polyps were seen or palpated and there were no other pathologic findings.

Choice of treatment—If a patient had passed per rectum polyps of grade 1 adenocarcinoma, but thorough exploration at laparotomy was negative, including examination of the lumen of the colon through two colotomies by sigmoidoscope, would you do:

1. Nothing further surgically, but follow patient by periodic barium enemas and sigmoidoscopic examinations?
2. A left colectomy with primary anterior anastomosis?
3. A total colectomy with ileoproctostomy?
4. A subtotal colectomy with cecoproctostomy?
5. A staged colectomy at first operation, i.e., (1) resection of sigmoid and descending colon with examination of opened resected colon for polyps, and if negative proceed with (2) resection of transverse colon, with examination of opened resected colon for polyps, and if negative proceed with (3) resection of remaining colon and ileoproctostomy?

Comment—The original microscopic examination of the expelled polyps revealed infiltration of the muscularis mucosae by the tumor. The entire blocked specimen was sent to the Armed Forces Institute of Pathology, which on July 25, 1956, reported:

"1. Basically, the lesion is interpreted as an adenomatous polyp. It shows, however, a few scattered foci of intraglandular budding and bridging, regarded as carcinoma *in situ*.

"2. More sections are being prepared from the block. If additional information is attained, it will be forwarded."

On November 9, 1956, the A.F.I.P. reported: "There are fairly numerous areas of intraglandular budding and bridging in these new sections, and there is considerably more carcinomatous change noted than in the original

*Captain L. L. Bean, M.C., USN, formerly Chief of Surgery, U.S. Naval Hospital, Corona, California, performed the surgery.

TABLE 1

ANSWERS TO QUESTIONNAIRE SENT TO SURGEONS

SURGEONS	CHOICE OF TREATMENT				
	1*	2†	3‡	4§	5‖
Dr. Herbert D. Adams, Lahey Clinic, Boston	x				
Dr. Nathaniel E. Adamson, Jr., Lahey Clinic	x				
Dr. Arthur W. Allen, Boston	x				
Dr. Joel W. Baker, Seattle	x				
Dr. Ralph F. Bowers, Memphis			x		
Dr. Alexander Brunschwig, Cornell University Medical College, New York	x				
Dr. Jack A. Cannon, University of California at Los Angeles School of Medicine					x
Dr. Richard B. Cattell, Lahey Clinic	x				
Dr. O. Theron Clagett, Mayo Clinic, Rochester, Minnesota	x				
Dr. Bentley P. Colcock, Lahey Clinic			x (second choice)		x (first choice)
Dr. Warren H. Cole, University of Illinois College of Medicine, Chicago				x	
Dr. George Crile, Jr., Cleveland Clinic, Cleveland	x				
Dr. J. Montgomery Deaver, Jefferson Medical College of Philadelphia	x (now)			x (at time of operation)	
Dr. Clarence Dennis, State University of New York College of Medicine at New York City, Brooklyn			x		
Dr. C. F. Dixon, Mayo Clinic	x				
Dr. Malcolm B. Dockerty, Mayo Clinic	x				
Dr. L. R. Dragstedt, University of Chicago School of Medicine					x
Dr. Herbert G. Dunphy, Boston	x				
Dr. Douglas A. Farmer, Boston University School of Medicine	x				
Captain H. Eighmy, M.C., USN, Camp Pendleton, California			x		
Dr. Henry Harkins, University of Washington School of Medicine, Seattle	x				

sections. The lesion is being coded as an adenomatous polyp with adenocarcinoma. The extent of the lesion cannot be determined from the microscopic preparations."

It is obvious from these reports that some pathologists might consider the lesion as carcinoma *in situ* or atypical hyperplasia. However, one area of the block of tissue did show invasion of the muscularis mucosae, which is almost uniformly considered the *sine qua non* of malignancy.

Serious consideration was given to the idea of polling some 30 pathologists, but this was abandoned. One eminent pathologist who reviewed the slides wished to remain anonymous "for several reasons, such as variances in terminology due to local custom, the fact that all pathologists do not get to see the same slides, and the fact that on borderline lesions such as this one the spread of terminology is terrific."

Comments From Replies to Questionnaire

Results of the survey are shown in table 1. The following comments were included in the replies received.

DR. HERBERT D. ADAMS: Here at the Lahey Clinic, our policy has always been No. 1.

DR. NATHANIEL E. ADAMSON, JR.: I would certainly be conservative. As you know, the pedicle left behind (presumably) might well not be involved; the patient would therefore have effected a "spontaneous cure."

DR. ARTHUR W. ALLEN: Procedure No. 1: Every three months for one year; every six

TABLE 1 *(Continued)*

ANSWERS TO QUESTIONNAIRE SENT TO SURGEONS

SURGEONS	CHOICE OF TREATMENT				
	1*	2†	3‡	4§	5‖
RESIDENT SURGEONS, University of Washington School of Medicine					
Dr. Mark B. Listerud	x				
Dr. John K. Stevenson	x				
Dr. George Girvin	x				
Dr. Roy Vetto					x
Dr. Tom W. Jones					x
Dr. John E. Jesseph		x			
Dr. James Tate Mason, Seattle	x (if no invasion)		x (if invasion)		
Dr. Charles W. Mayo, Mayo Clinic	x				
Dr. John B. McKittrick, Boston			x		
Dr. John H. Mulholland, New York University College of Medicine, New York	x				
Dr. Isador S. Ravdin, Philadelphia		x			
Dr. Cornelius E. Sedgwick, Lahey Clinic					x
Dr. Neil W. Swinton, Lahey Clinic	x				
Dr. Grantley W. Taylor, Harvard Medical School, Boston	x				
Dr. Waltman Walters, Mayo Clinic	x				
Dr. Kenneth W. Warren, Lahey Clinic	x				
Dr. Owen H. Wangensteen, University of Minnesota Hospitals, Minneapolis			x		
Dr. John M. Waugh, Mayo Clinic	x				
Dr. Claude E. Welch, Boston					x
Dr. Nathan Womak, University of North Carolina, Chapel Hill	x				

*Nothing further surgically, but follow patient by periodic barium enemas and sigmoidoscopic examinations.

†A left colectomy with primary anterior anastomosis.

‡A total colectomy with ileoproctostomy.

§A subtotal colectomy with cecoproctostomy.

‖A staged colectomy at first operation, i.e., (1) resection of sigmoid and descending colon with examination of opened resected colon for polyps, and if negative proceed with (2) resection of transverse colon with examination of opened resected colon for polyps, and if negative proceed with (3) resection of remaining colon and ileoproctostomy.

months the second year, and every year thereafter. Procedure No. 2: No. How do you know the polyps came from the left side? Procedure No. 3: Too radical now. Procedure No. 4: Same as No. 3. The intraluminal examination with sigmoidoscope rules out a large cauliflower lesion that had sloughed off a couple of portions. Also, this and the barium enema rule out multiple polyps.

An unusual case. I have seen this situation with one sloughed-off polyp twice; one was resected between films taken six weeks before [which] gave us the location. The pathologist could find no residual [tissue] and could not identify the original site.

DR. JOEL W. BAKER: Favorable prognosis. I agree with what has been done; No. 1 from this point on. Blind major resection is not justified. Seventy-five per cent chance of origin in lower sigmoid or rectum, and this area should be 'scoped frequently.

DR. RALPH F. BOWERS: No. 3. A total colectomy with ileoproctostomy or lower sigmoid. It is possible to miss a small source after polyps passed. Colectomy and then proctosigmoidoscopic examinations at frequent postoperative intervals.

DR. ALEXANDER BRUNSCHWIG: At laparotomy, did you make several colotomies and look into colon with a proctoscope?

DR. JACK A. CANNON: No. 5. A staged colectomy. I would leave as much sigmoid as could be reached by sigmoidoscopy. This choice would assume that the stomach was negative to exploration.

DR. RICHARD B. CATTELL: I dislike very much to give an opinion relative to your patient without being able to review the slides and x-rays. In view of the negative exploration and negative visualization of the lumen of the colon at the time of exploration, I would repeat sigmoidoscopic examinations, barium enemas and contrast enemas once a month for the next three months. If I were satisfied with the repeat barium enema showing a definite lesion in the distal end of the transverse colon, I would resect the left half of the transverse colon, descending colon, and do a primary anastomosis between the transverse colon and low sigmoid.

DR. BENTLEY P. COLCOCK: Most interesting. You will probably get varied answers. Since this was an invading lesion, I think you have to do at least No. 5. If you still cannot be sure that you have resected the area from which the carcinoma came, I would do No. 3, saving all the ileum possible.

DR. WARREN H. COLE: You certainly have a very interesting problem and one which will, no doubt, be controversial. I have marked No. 4 as my suggestion for therapy.

DR. GEORGE CRILE, JR.: Grade 1 carcinoma of the colon, whether treated or untreated, is consistent with long and happy life. The real question here is whether it is really a grade 1 cancer. It seems to me that the questionnaire should be sent to 30 pathologists instead of 50 surgeons.

DR. J. MONTGOMERY DEAVER: I would do nothing except follow the patient with colon x-rays and sigmoidoscopic examinations. I am not sure, but rather feel that I would have been tempted to resect the colon, that is, the midtransverse to low rectosigmoid, at the time of operation.

DR. CLARENCE DENNIS: I would favor colectomy with ileoproctostomy, leaving only as much rectum and sigmoid as can be closely followed by proctoscopy. I should have done this as the initial operation, as the use of colotomy and 'scope has been unreliable in my hands.

DR. C. F. DIXON: I have received a copy of your record of the patient who supposedly passed polyps per rectum. I must say that the entire story sounds a bit peculiar to me.

Bleeding that comes from polyps is usually red, unless the polyps are located in the small intestine. The facts that the patient felt weak, dizzy and faint and that the blood was dark would make me suspicious that the bleeding came from the stomach or duodenum.

Having carried out an abdominal exploration as you did and viewing the colon through two colotomies and finding it negative, my feeling would be to do nothing, because if the polyp should recur, it would not do so, in my experience, in a metastatic fashion, but merely recur in the original site as a recurrent polyp. Personally, after what has been done after negative findings, I would consider a subtotal colectomy.

Finally, I also would want to question this woman very carefully as to whether or not the bleeding might have been coming from the uterus. She could have had a polypoid mass slough from the body of the uterus, in which case she would, of course, have had intermenstrual bleeding.

DR. MALCOLM B. DOCKERTY: I would like to examine the specimen to rule out possibility of its being of uterine origin. I have seen two instances of colonic cancers "curing" themselves by sloughing completely.

DR. HERBERT G. DUNPHY: I would be inclined to wait for further evidence of cancer to occur, getting a barium enema every six weeks and repeating the sigmoidoscopic examination. If in six months' time I still could not identify the source of the tumor, I would re-explore for a second look.

DR. DOUGLAS A. FARMER: Thank you for sending me the transcript of your very interesting case. My immediate reaction was that I was unusually glad the patient is your problem and not mine. It is certainly frustrating enough to get into an abdomen knowing that there is a bleeding point somewhere and to be unable to find it, let alone to go in knowing there is cancer and be unable to localize it.

I think, in retrospect, I would have done exactly what you have done up to this time; namely, after the completely negative exploration I would probably have felt obliged to close the abdomen. Although you did not say so, I assume you explored her from "stem to stern," keeping in mind the colonic mucosal membrane rests in the smaller bowel or even in the duodenum or stomach. This brings up one point, of course; namely, how certain the pathologist is that this is colonic carcinoma rather than carcinoma somewhere else in the gastrointestinal tract. I would be inclined to check her at least monthly with barium enemas and sigmoidoscopic examinations as well as with careful upper gastrointestinal and small bowel series for approximately four to six months. If by that time I had still been unable to localize the lesion, I would feel obliged to re-explore her. If the same thing happened again, namely, no evidence of origin of the disease, I would close her again without extensive bowel resections, then would repeat the same procedure for another six months. Very rarely, of course, cancers do cure themselves by simply outstripping their blood supply and sloughing away *in toto*.

DR. HENRY HARKINS: I believe the case outlined in your questionnaire is a very interesting one, and certainly the decision is indeed difficult. I circulated this to several of my top residents and received a number of answers. I thought you would be interested in all of them. They are as follows:

DR. MARK B. LISTERUD: First, I would like to be sure that the pathologist means by gastrointestinal adenocarcinoma the type of atypia which is frequently seen in polyps of the colon. Secondly, I would like to be sure that the roentgenologist can produce good double contrast films. If the above conditions are present, I believe the patient would be best served by conservative therapy with sigmoidoscopy and double contrast studies every three months.

DR. JOHN K. STEVENSON: The problems produced in this case history are indeed complex. Statistically, I agree that there is a good chance of removing the site from which the polyps originated by a left colectomy. I do not feel that this could be applied to an individual case; however, I feel that there is a good chance that more polyps may still be present in the colon. These can *easily be missed* by barium studies and surgical exploration. There is the possibility that the patient sloughed her entire tumor at the original episode. I feel that the only two suggestions made that are practical in this patient are Nos. 1 and 5.

At present, from experience so far in my training, I favor the first choice (No. 1). I would want to have the responsibility of doing the sigmoidoscopic examinations myself and have complete confidence in the person performing and interpreting the barium studies on the colon.

The examinations should be frequent and repeated immediately should any suspicious findings be made. If these were confirmed by further examination I would advise operation and exploration.

DR. GEORGE GIRVIN: Thank you for presenting us with this interesting case. With one recent exploratory laparotomy which failed to reveal the sites of extruded carcinomatous polyps by palpation or colectomy, I would favor periodic examinations by sigmoidoscopy and barium enemas. It is conceivable that all of the tumor tissue was passed, but if recurrences present themselves, they can be readily demonstrated in time for a curative resection.

DR. ROY VETTO: My thoughts regarding the "clinical case" are as follows: Remembering that (1) the patient had cancer; (2) the cancer is probably curable; and (3) the loss of a portion or all of her colon is a fair price to pay for a cure, I would favor the fifth choice with the following stipulations. (1) Prior to surgery, sigmoidoscopy should be repeated by a different operator (or operators). (2) At operation, another attempt should be made to locate the source by use of the sigmoidoscope and multiple colotomies. (3) If the staged resections are necessary, each stage should be performed as a curative procedure.

DR. TOM W. JONES: Because of the difficulty involved in the localization of a polyp or, in this case, the remaining stalk of a polyp in the colon, I think sigmoidoscopy and barium enemas should be repeated. I also believe the pathologic specimen should be reviewed

(pathologic slides). If these diagnostic studies are still unproductive, a staged colectomy should be performed and the specimen examined by the pathologist. The first stage should include the descending colon and the sigmoid, for I believe the lesion to be from that area.

DR. JOHN E. JESSEPH: Since the site of tumors is unknown, no definitive "curative" procedure can be done, although the one most apt to be curative would be total colectomy. This is *not* indicated. I would think that the patient should be subjected immediately to a radical descending and left transverse colectomy, with frequent barium examinations thereafter.

DR. HARKINS: As you see from the six comments, three of them are for the first choice, that is, careful follow-up at periodic intervals; one is for the second choice, namely, left colectomy with anterior anastomosis, and two are for the fifth choice, a staged colectomy at the first operation. I believe that I would go along with the first choice but be very insistent that this is done at frequent intervals at first, gradually becoming less frequent later. I would also partly put it up to the patient as to which of the choices would be adopted.

DR. JAMES TATE MASON: Step sections through the lesion to determine question of invasion. Then, if no invasion, I would prefer No. 1; if invasion, I would prefer No. 3.

DR. CHARLES W. MAYO: I think the assumption that it was a pedunculated polyp and that the pedicle or at least a portion of it remains is a good one.

Since the sigmoidoscopic examination showed negative findings, I doubt that such examinations need be repeated more than once a year. However, as far as x-ray examination is concerned, I think a contrast roentgenogram should be made every three months for at least one year and then every six months for two or three years, unless something showed up in the interim.

These polyps are of low grade and slow-growing, and the only question is whether a remnant of the malignant portion of the polyp remains which is too small at present to be recognized. Without roentgenographic evidence of its presence, I would be against any further operative procedure to search for the condition and would prefer periodic roentgenographic examinations for this purpose.

DR. JOHN B. MCKITTRICK: The problem you have posed regarding the patient who sloughed off the malignant polyps of the colon is indeed a very interesting one.

Without knowledge of the site of the origin of the tumor, it is not possible to recommend segmental resection of the colon with sufficient assurance that the "right" segment of the bowel will be removed. From the protocol, it seems that the sigmoidoscopy was done within 24 hours and nothing abnormal was seen in the distal bowel. This is good evidence the tumor came from higher up, but it is not conclusive evidence.

The only procedure which will assure removal of the site of the origin of the tumor is total removal of the large bowel and permanent ileostomy. I would, however, give enough credit to the sigmoidoscopic findings to believe the rectum (from the level of the middle hemorrhoidal vessels) could be preserved with very little risk of leaving tumor in the wall of the bowel.

I would tell the patient I did not know whether there was residual tumor present and that there was nothing further we could do to find out. I would further say that there was a "gambler's chance" that no further tumor remained. If the patient wished to accept this gamble, she would have no further surgical procedure. If the patient wished that everything reasonable be done to assure removal of residual disease, I would advise total abdominal colectomy and ileoproctostomy. The distal resection margin should be below the pelvic floor, thus sacrificing the superior hemorrhoidals and preserving the middle hemorrhoidal vessels.

There is a risk of being wrong no matter what is done in this instance. It becomes, then, a matter of opinion which course gives the smallest calculated risk for the greatest benefit.

DR. CORNELIUS E. SEDGWICK: The pathology report indicates that the muscularis mucosae is infiltrated by tumor. Therefore, we must assume that a tumor persists, and No. 1 choice,

that of wait and watch, must be discarded and operation advised. The fact that bright blood and pieces of tissue (polyps) were passed without feces suggests the left colon rather than the right colon as the origin of bleeding. Furthermore, the incidence of polyps in general is greater in the left colon than in the right. However, we are not sure that these polyps originated in the left colon; therefore, the No. 2 choice, that of left colectomy and primary anastomosis, must be discarded. A subtotal colectomy with cecoproctostomy (choice No. 4) must also be discarded, because polyps may occur in the cecum, and there is no advantage of this operation over an ileoproctostomy.

We then have left two choices: total colectomy with ileoproctostomy (choice No. 3) or a staged colectomy (choice No. 5). Because we are dealing with a relatively low-grade malignancy, I would not like to subject the patient to total colectomy (ileoproctostomy) if it was not absolutely necessary to effect a cure. It is frequently difficult in a patient with total colectomy to regulate bowel movements or to maintain nutrition. Therefore, I would select as the procedure of choice a staged colectomy.

The first resection would consist of the sigmoid-descending colon, splenic flexure and left transverse colon. I would like to have this specimen carefully examined immediately by a competent pathologist. If the origin of the polyp was found, I would do a primary anastomosis of the transverse colon to the lower sigmoid. If tumor was not found, then I would proceed with a total colectomy and an ileoproctostomy.

DR. NEIL W. SWINTON: Your letter and case history present an interesting problem.

We have had several similar situations here at the Lahey Clinic, although they are, of course, extremely rare and probably most common in children. I would see no reason whatsoever to do any further surgery on this patient, if you have the utmost confidence in your department of radiology and are thoroughly convinced of what your pathologists term as a grade 1 adenocarcinoma. I assume that that does mean, both from the term and from the description of the tumor, that the tumor shows definite invasion. I do not believe that anaplasia, irregularity of architecture, and so forth in many of these polypoid tumors are too significant, although one cannot escape the diagnosis of cancer if definite invasion is present.

If sigmoidoscopic and repeated and adequate x-ray studies of the colon are negative, I personally would not particularly worry too much about the prognosis. In our own experience here at the Clinic the feeling is that such examinations will pick up an early tumor about as soon or sooner than will abdominal exploration.

DR. KENNETH W. WARREN: I would request a review of the microscopic analysis of the extruded tissue. If the diagnosis of grade 1 malignancy is sustained, repeated air contrast enemas with multiple-angle views should be performed on two or three occasions. If these x-rays show consistently questionable polyps in the region where they formerly were thought to be present, a resection of that portion of the bowel should be performed. I would oppose blind resection of any portion of the colon unless strong suspicion could be directed toward a given area.

In evaluating this problem further, one must not lose sight of the possibility that this malignant adenoma came from higher in the gastrointestinal tract. Careful x-rays of the stomach and small bowel should be pursued before any further surgery is performed.

If no suspicious areas can be demonstrated anywhere along the gastrointestinal tract, I would be inclined to do periodic studies and no further exploration unless suggestive localization could be determined by x-ray studies.

DR. OWEN H. WANGENSTEEN: At the time of the initial operation, I would have done a near subtotal or near total colectomy, resecting the colon a few centimeters below the cecal promontory (well below the 25 cm. level of the sigmoidoscopic examination). A look into the cecum at the time of operation would serve to satisfy the surgeon that the cecum was either free or a likely source of the sloughed lesion. In any case, contingent on circumstances, I would have then proceeded to anastomose either the terminal ileum or the ascending colon a few centimeters distal to the ileocecal

valve to the iliac colon a few centimeters proximal to the true rectum.

As for the present course of action, in the light of the negative proctoscopic and barium studies as well as a negative exploratory examination, I would assume that it would be safe to sit and wait. The only other alternative would be to do exactly what I have outlined.

DR. JOHN M. WAUGH: Even if positive for polyps you have no assurance this was the site of the slough. Can you be sure these came from above the rectum? Monthly proctoscopic examinations and colon x-rays should soon show lesion if there was invasive cancer left. I prefer course No. 1.

DR. CLAUDE E. WELCH: I have checked one of the alternatives that you have suggested, but since I would not follow that routine exactly, I will comment on it more in detail.

From your description, I think it is fair to assume that the patient is a good operative risk and that the diagnosis of carcinoma has been confirmed by a consulting pathologist. Under those circumstances, I would have proceeded with a partial colectomy at the first operation. The point at which the bowel would be sectioned distally would not have been in the rectum, because it may be assumed that the distal 25 cm. could not be the site of the polyp. From that point in the low sigmoid, I would mobilize the left colon and the distal transverse colon, removing this as a single specimen. If the examination then showed the base of the polyp, I would do nothing more. If it were negative, I would remove the rest of the colon and do an ileosigmoidostomy.

I think it is quite important to save as much of the rectum and lower sigmoid as possible, since, if an ileoproctostomy is made at too low a level, chances of serious diarrhea are high.

Discussion

It is not the purpose of this presentation to discuss the individual opinions of the surgeons who answered the questionnaire. Each had sincere reasons for his judgment, based on extensive experience, study and thought of the problem, all of which constitute his philosophy of cancer of the colon. It is evident that there is a significant difference among surgeons in the approach to such a problem case of cancer of the colon if 21 (60 per cent) would not have performed any type of resection after thorough exploration, including colotomy and colonoscopy, and 14 (40 per cent) would have resected part or all of the colon in an attempt to remove any remaining focus of cancer and other polyps if present. In this case, the pathologist, the surgeon and I agreed that the muscularis mucosae of the sloughed polyp was invaded by cancer cells and that the diagnosis was cancer.

It is realized that conclusions drawn from the results of a mailed questionnaire on a clinical case problem such as this may be inaccurate to a degree due to two factors: (1) a variant in the perception of the points of the problem presented in the printed form and (2) a variant of decreased interest induced by a questionnaire compared with the interest in a live patient. However, it may be inferred that the high diagnostic acumen and clinical interest of the listed surgeons in a dry case presentation would be a function of the conclusions, and any variance of perception or interest would be voided in the final analysis.

The concept of the etiology of cancer of the colon is based on the study of the life history of adenomatous polyps of the colon. Although there is no known method to determine whether or when a histologically benign neoplastic polyp will develop a frankly malignant growth, there no longer can be any doubt that cancer of the colon originates in the seed bed of a polyp in a very high percentage of cases. There should be few surgeons today who have not seen the early transition of a benign polyp into an invasive malignant one. Dukes believes that an adenoma results when neoplastic cells derive from the deeper layers of glandular epithelium lining the intestinal mucous glands at the bottom of the crypts of Lieberkühn. Swinton[1,2] subscribes to the neoplastic etiology of benign polyps and classes them as true tumors that must be considered premalignant lesions which are the result of some inherent defect of cellular growth, not the result of an inflammatory process. Virchow hypothesized that a hyperplastic response to inflammation produces polyps, and Verse, Genkin, Hoelzel

et al. suggested that chronic inflammation or irritation in the presence of a congenital predisposition for neoplasia was necessary for the production of polyps.

More recent studies in cellular metabolism in relation to cancer have demonstrated that cellular injuries which interfere with the normal oxygenation process within the cell may well be a determining factor inciting malignant changes.

The diagnosis of malignant change or frank cancer in an adenomatous polyp may be difficult at times and result in distinct differences of opinion when the same slide is viewed by more than one pathologist. A slide was submitted to four pathologists,[3] and the following diagnoses were given: (1) benign adenoma; (2) grade 1 adenocarcinoma, benign; (3) carcinoma *in situ*; and (4) atypical adenoma. This is a familiar pattern, and surgeons and pathologists have repeatedly made their pleas for a common denominator of terms.

The treatment of carcinoma of the colon and rectum has evolved from the pre-1908 era of the Paul (1892) and Mikulicz (1902) segmental resections, when the advance made by these masters involved the removal of the primary growth with a lowered operative mortality, to the post-1908 Miles era, in which attention has been increasingly given to the metastatic areas in the mesentery. When Rankin developed his obstructive resection at the Mayo Clinic, it was possible to resect more node-bearing mesentery with further decreased mortality. The current philosophy of realistic surgeons regarding cancer of the colon and rectum tends toward a concentrated interest in extending the surgical removal of mesenteric vascular-lymphatic node-bearing tissue.

In view of the repeated demonstration of more than 50 per cent lymphatic metastases for over three decades, simple segmental resection cannot be reasonably justified. Lillehei and Wangensteen[4] have repeatedly been quoted for their advocacy of subtotal colectomy with cecoproctostomy and total colectomy with ileoproctostomy for patients with polyps or cancer of the colon. They would seem justified in their philosophy, since they reported residual cancer in 43 per cent of patients with rectal cancer and in 48 per cent of patients with cancer of the colon. Of 73 patients who had total or subtotal colectomy, 38 per cent had unsuspected polyps or cancer; of 43 patients with cancer of the colon, three (7 per cent) had a second cancer not diagnosed preoperatively. Ginsburg and Dreiling[5] reported an incidence of 3.5 multiple carcinomas in 700 bowel resections. Bargen[6] encountered two or more carcinomas in 4.6 per cent of 344 cases of cancer of the large bowel. Mayo and Schlicke[7] in 1942 reported on 131 autopsies performed within three weeks of operation for cancer of the colon and rectum; 49 patients (37.4 per cent) had polyps in the remaining colon, and there was a second carcinoma in 5.3 per cent.

Some surgeons view the developing philosophy of surgery for cancer as an advancing behemoth, crippling and mutilating all in its path. A loyal opposition, to act as a brake on premature application of experimental radical surgery, is healthy and desirable. Crile[8] is probably foremost in this category. He believes that "there is a growing tendency to lump cancers together as a surgical disease and to apply ultraradical treatment to nearly all patients with cancer," and that "in some of our specialized hospitals, along with the practice of ultraradical surgery for cancer, there has developed a philosophy that the presence of cancer justifies anything that the surgeons elect to do."

Slaughter,[9] on the other hand, believes that "if recurrence and death from cancer were immediate and dramatic, our sense of personal responsibility would be kept taut, but the time lag in the disease allows slackening, so that too often the surgeon takes the line of least resistance from the beginning instead of the line of most resistance; the serious treatment and evaluation of cancer patients is a grim business."

Ravdin[10] states that "in spite of the interest, research and increasing knowledge as to the origin, behavior and spread of such cancers (large bowel carcinoma) there is considerable reluctance to accept methods of surgical treatment best suited to diagnose and treat which will provide the maximal survival. The

philosophy of cure, once the diagnosis has been made, has not received general acceptance. The time may well come when our successors may conclude that much of our thinking has been superficial. The mandate of the surgeon is clear and unequivocal. He must search himself to determine if the motives which lead him to do lesser conservative operation for a disease which can reasonably be expected to kill the patient are not conditioned by (predicated on) a fearsome pride in having a live patient, if only temporarily. Sympathy has no place in the armamentarium of the surgeon once the clean-cut indications of cancer surgery are present."

Scarborough[11] expressed his philosophy clearly: "In the course of continuing follow-up studies of all patients who have had one or more polyps of the colon, we find an increasing percentage of patients in whom new polyps and even new cancers have developed. This has gradually brought us to the position where we are dissatisfied with our surgical procedure in any polypoid disease of the abdominal colon short of complete abdominal colectomy. I say that we are dissatisfied. We have not yet had the courage of any conviction that in every patient with an adenomatous polyp in the abdominal colon we should perform complete abdominal colectomy with preservation of the rectum and anastomosis with the ileum. Yet, in our own minds we are approaching that thought, because as we learn more and more of these adenomatous lesions we realize the high percentage of multiplicity and the high frequency of the development of new lesions. We know they can 'sneak up on you,' and can become malignant before there are any signs or symptoms or before they can be found by any of our ordinary methods of investigation. Certainly the one sure way of preventing the development of new adenomatous lesions of the colon is to remove the colon. Today, from the point of view of surgical technic, abdominal colectomy with primary anastomosis is not a difficult procedure. It is not particularly hazardous and we probably will arrive at the conclusion eventually that abdominal colectomy should be performed when an adenomatous polyp is present."

Therefore, since medical science is not an exact science and since the biologic behavior of cancer is such a complex of reaction, interaction, inherent susceptibilities, predispositions and biohistochemical variability in the individual, the therapeutic approach to the problem of cancer at the present status of our knowledge must be predicated on the accumulated collective experience with the pattern of each type of cancer.

The individual surgeon's interpretation and application of conclusions drawn from this collective experience will be framed and influenced by his philosophy of life and death, by the ratio of sympathy and scientific objectivity he has developed, and by the degree of intellectual honesty and prejudice he possesses.

Summary

1. The history and the physical, laboratory, x-ray and surgical findings of a 49 year old woman who passed two red liquid bloody stools and who recovered from the second bloody stool two fragments of globular tissue were presented in a questionnaire sent to 50 surgeons.

2. The pathologic report on the tissue recovered was "polypoid, well-differentiated adenocarcinoma with no pedicle and consisting of neoplastic colonic mucosa dispersed around a central core of fibrous tissue and *muscularis mucosae* infiltrated by tumor. Diagnosis: grade 1 adenocarcinoma of the colon." The diagnosis was substantiated by the Armed Forces Institute of Pathology.

3. After two sigmoidoscopic examinations and two air contrast barium enema x-ray studies, the last of which was suggestive of two radiolucent areas in the distal end of the transverse colon which might have represented polyps, an exploratory laparotomy was performed. At operation, the findings in manual and visual inspection of the viscera were within normal limits.

4. Two colotomies were made, and the colon was inspected directly through a sigmoidoscope. A suspicious area was seen in the lower sigmoid, and 20 cm. of the lower sigmoid was resected segmentally. Inspection of the open resected colon was negative for residual

polyps. Nothing further was done, and the patient made an uneventful recovery.

5. Follow-up periodic sigmoidoscopic and barium enema studies were negative up to February 1958, and the patient was well at that time.

6. Thirty-five surgeons, representing an academic and geographical cross section of the country, responded to the questionnaire and indicated their opinions as to what should have been done at the time of the exploratory laparotomy. The results of the poll are given in table 1.

7. Sixty per cent of the surgeons answering the questionnaire were against blind resection for possible residual cancer in a polyp or polyps; 40 per cent were in favor of some type of resection of the colon.

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Pituitary Insufficiency: A Clue to the Diagnosis of Sellar Tumors

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Pituitary insufficiency indicates disease in the region of the sella turcica and hypothalamus. Tumors of this region may cause pituitary insufficiency.

A finding such as diabetes insipidus, or even amenorrhea, should alert the physician to the possibility of a pituitary tumor.

Diagnosis may require such additional evidence as visual-field or x-ray changes.

HISTORICALLY speaking, the importance of endocrine changes in the recognition of pituitary disease is emphasized by the fact that the first pituitary disease entity to be described was that of acromegaly, mentioned originally by Marie in 1886 and later shown to be due to oversecretion of growth hormone by the eosinophilic adenoma. Along with Simmonds' description of the less striking syndrome of severe insufficiency of the anterior lobe of the pituitary gland, others began to notice that "women with unaccountable amenorrhea not infrequently complained of disturbances of sight."[1] The discovery of these associated changes in the visual fields as well as x-ray evidence of erosion of the pituitary fossa in such patients led Cushing and other pioneer neurosurgeons to demonstrate that many such instances of hypofunction of the pituitary gland are due to destruction of the gland by chromophobe adenomas, craniopharyngiomas and other tumors.

In addition it became apparent that the anterior and posterior lobes of the pituitary gland serve different functions. The anterior lobe became known as the "master" gland which controls growth and the "target" glands, that is, the thyroid, adrenals, gonads and mammary glands. The posterior lobe was found to secrete hormones which contain antidiuretic, oxytocic and vasopressor properties.

Recent findings suggest that the hypothalamus plays an important role in the function of both lobes of the pituitary. There has been considerable evidence to support the theory that antidiuretic hormone is produced in the hypothalamus, migrates down the nerve fibers of the supra-opticohypophyseal tract in the pituitary stalk, and is stored in portions of the pituitary stalk and posterior pituitary lobe.[2]

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Thus the median eminence, pituitary stalk and posterior lobe of the pituitary gland have become known as the neurohypophysis and are considered to be a functional unit under the control of the hypothalamus. Likewise animal work and certain clinical syndromes associated with tumors involving the hypothalamus and manifested by abnormalities in sexual development have suggested that the anterior pituitary lobe is also controlled, at least in part, by the hypothalamus. As no nerve fibers are known to extend from the hypothalamus to the anterior pituitary lobe, it has been postulated that such hypothalamic control takes place by secretions which are thought to originate in the median eminence or hypothalamus. These supposed hormones are thought to find their way to the anterior lobe by way of the portal blood system which originates in the median eminence and courses down the pituitary stalk to terminate in the sinuses of the anterior lobe of the pituitary gland.[3]

Encroachment on the pituitary or hypothalamus by tumors may result in failure of the anterior or the posterior lobe of the pituitary, or both. Usually the diagnosis in such cases is not difficult. One often finds x-ray changes in the form of erosion of the pituitary fossa or calcification in the suprasellar region. Bitemporal defects in the visual fields are the classic eye signs of an expanding pituitary tumor. Variations of this may be found in those cases where such lesions originate outside or have extended out of the sella turcica. However, tumors in this region are not invariably associated with abnormal visual-field findings, neurologic signs and symptoms, or x-ray changes. In fact, the symptoms and signs of pituitary insufficiency may be on occasions the only evidence of disease in this region.

Thus the problem of diagnosis in cases of tumors in which pituitary failure is the only finding raises some important questions, three of which we should like to discuss. They are: (1) What are the classic signs and symptoms of pituitary insufficiency in adults? (2) What are some of the causes of pituitary insufficiency? (3) What important single findings of pituitary insufficiency should alert the clinician to the possibility that there may be a tumor in the region of the sella turcica?

What Are the Classic Signs and Symptoms of Pituitary Insufficiency in Adults?

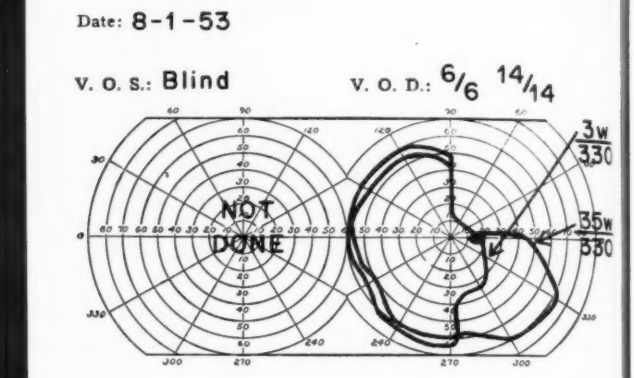
As has been mentioned previously, the pituitary gland is divided into two main functional units, the anterior lobe and the neurohypophysis which includes the posterior lobe. Clinical evidence of anterior pituitary insufficiency will depend on the amount of the anterior lobe that is destroyed. Classically, a growing tumor of the intrasellar region affecting the anterior lobe will cause failure of the gonads first, followed by declining function of the thyroid gland and finally the adrenal cortices.[4]

Consequently, in women an early symptom is amenorrhea. In men the prostate may become small and the testicles atrophied. Both sexes will complain of decrease or loss of libido. The pituitary gonadotropins may be decreased or absent.

As the anterior pituitary insufficiency progresses, the skin becomes yellowish, pale and somewhat wrinkled and may appear myxedematous. The eyebrows, beard, axillary and pubic hair may become very scanty.

The basal metabolic rate is usually quite low and the blood cholesterol may be increased. Mild anemia may develop. The protein-bound

FIGURE 1. Roentgenogram in a typical case of pituitary tumor with anterior pituitary insufficiency.



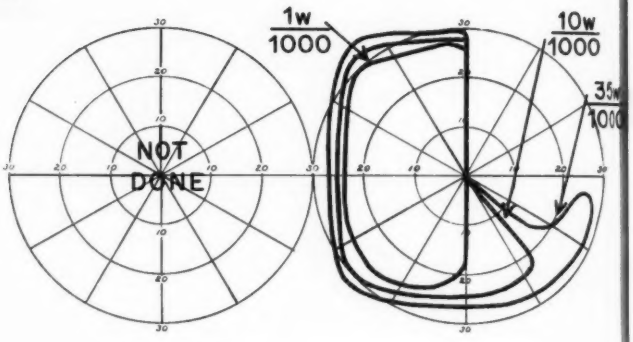


FIGURE 2. Visual fields in the case represented in figure 1.

iodine may be decreased and there is poor concentration of radioactive iodine in the thyroid. The urinary excretion of 17-ketosteroids and corticosteroids may be decreased and the patient becomes markedly sensitive to insulin, or even may have spontaneous, symptomatic hypoglycemia. The typical findings of anterior pituitary insufficiency secondary to a pituitary tumor are illustrated by the following case.

Case 1—A 34 year old woman was admitted to the Mayo Clinic with the complaints of headaches and spotty vision for seven years and blindness of her left eye for five years. During the three years before admission she had menstruated only three times. For the past year or two she had noticed intolerance to cold, dryness of the skin, thinning of the pubic and axillary hair, and puffiness of the eyelids. X-ray examination of the head revealed decalcification of the dorsum sellae, floor of the sella, and anterior clinoid processes with poorly defined suprasellar calcification (figure 1). The left eye was blind. Visual-field examination of the right eye revealed almost complete temporal anopsia. These visual defects indicated a chiasmal lesion (figure 2).

Urinary pituitary gonadotropins and 17-ketosteroids were absent. The urinary corticosteroids measured 0.45 mg. per 24 hours. The basal metabolic rate was –29 per cent, and the plasma cholesterol, 251 mg. per 100 cc. The specific gravity of the urine was 1.015. At operation a large pituitary chromophobe adenoma was found.

As will be discussed later, posterior pituitary insufficiency, that is, diabetes insipidus, rather than anterior pituitary insufficiency, may occur if the tumor or other type of lesion

involves the neurohypophysis (or its connections in the hypothalamus) first and may be the presenting complaint.

What Are Some of the Causes of Pituitary Insufficiency?

In the table are listed a number of causes of pituitary insufficiency or failure. The most

SOME CAUSES OF PITUITARY INSUFFICIENCY

Chromophobe adenoma
Craniopharyngioma
Eosinophilic adenoma
Pinealoma
Other tumors
Aneurysm
Postpartum necrosis
Other vascular lesions
Cavernous sinus thrombosis
Infections of the sellar region
Trauma
Xanthomatosis
Sarcoidosis
"Idiopathic"

common tumor is the chromophobe adenoma of the pituitary. The craniopharyngioma is also a cause of pituitary failure, both anterior and posterior. The eosinophilic adenoma also may be associated with decreased function of the anterior pituitary gland. Sarcoidosis may cause anterior pituitary failure as well as diabetes insipidus, which may be transient.

Destruction of the pituitary gland may occur during head injuries or meningitis. In such cases varying degrees of anterior pituitary failure as well as diabetes insipidus may result. Necrosis of the anterior pituitary lobe may occur post partum, but diabetes insipidus is rare in such instances.

In a certain number of cases, anterior or posterior pituitary insufficiency or both may occur with no x-ray, neurologic, physical or visual-field evidence of sellar or parasellar disease. Whether the insufficiency in such cases is due to disease inside the sella turcica, such as a tumor, or whether in some cases it is related to dysfunction of the pituitary stalk and hypothalamus is not known. From a practical standpoint it is impossible to differentiate such cases from those in which the tumors are too small to be identified. Consequently it is important to follow all such patients at regular intervals.

What Important Single Findings of Pituitary Insufficiency Should Alert the Clinician to the Possibility of a Tumor in the Region of the Sella Turcica?

As pituitary insufficiency may precede rather than follow x-ray or visual-field changes in tumors of the sellar region, the clinician should be alert to single signs or symptoms of pituitary insufficiency which may eventually prove to be a clue to the diagnosis. Such a single symptom, amenorrhea, that eventually led to the diagnosis and treatment of a pituitary adenoma is illustrated by the following case.

Case 2—A 22 year old woman was admitted to the Mayo Clinic in 1951 with the complaint of amenorrhea for two years as well as obesity (212 lb.). No other evidence of pituitary insufficiency could be found. X-ray examination of the head gave normal results. There were no visual complaints. The specific gravity of the urine was 1.028. The basal metabolic rate was –8 per cent. The urinary corticosteroids measured 0.49 mg. per 24 hours, and the 17-ketosteroids, 9.4 mg. per 24 hours.

Because of the lack of significant findings the patient was given a reducing diet and asked to return at regular intervals. However, she did not return until 1954, when she complained of loss of libido for nine months and decreasing vision in both eyes for two months. Her weight was 223 lb. X-ray examination of the head gave normal results (figure 3). Examination of the visual fields revealed almost complete bitemporal hemianopsia with loss of central vision in the right eye (figure 4).

The specific gravity of the urine was 1.027. The basal metabolic rate was –9 per cent; the plasma cholesterol was 420 mg. per 100 cc. The urinary corticosteroids measured 0.74 mg. per 24 hours, and the 17-ketosteroids, 9.4 mg. per 24 hours. No pituitary gonadotropins were present in the urine. At operation a mixed-type pituitary adenoma was found.

In this case amenorrhea was the presenting symptom of anterior pituitary insufficiency and the clue to the correct diagnosis. When

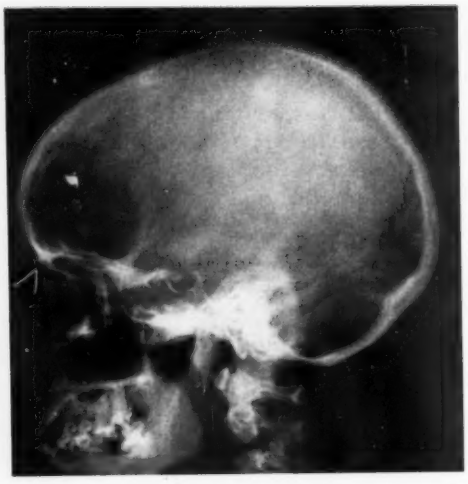


FIGURE 3. Normal x-ray appearance in a case of mixed-type pituitary adenoma.

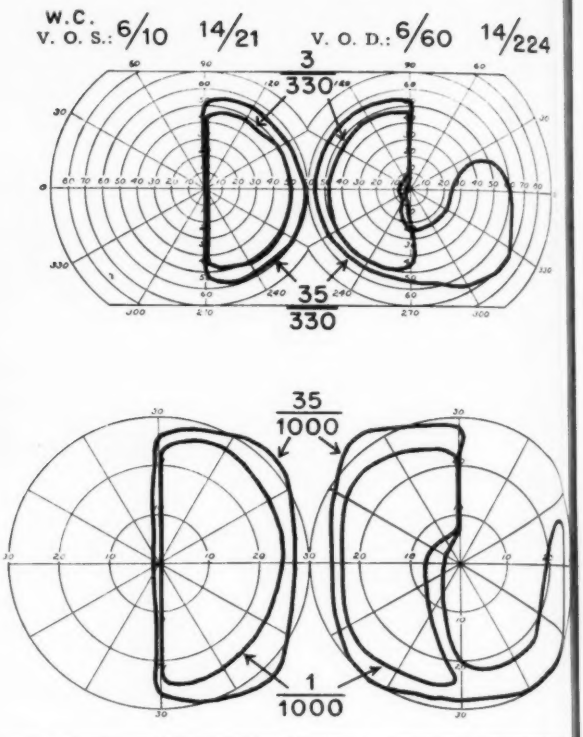


FIGURE 4. Visual fields in the case represented in figure 3, revealing almost complete bitemporal hemianopsia with loss of central vision in the right eye in a patient whose initial complaint of amenorrhea preceded the visual-field loss by five years.

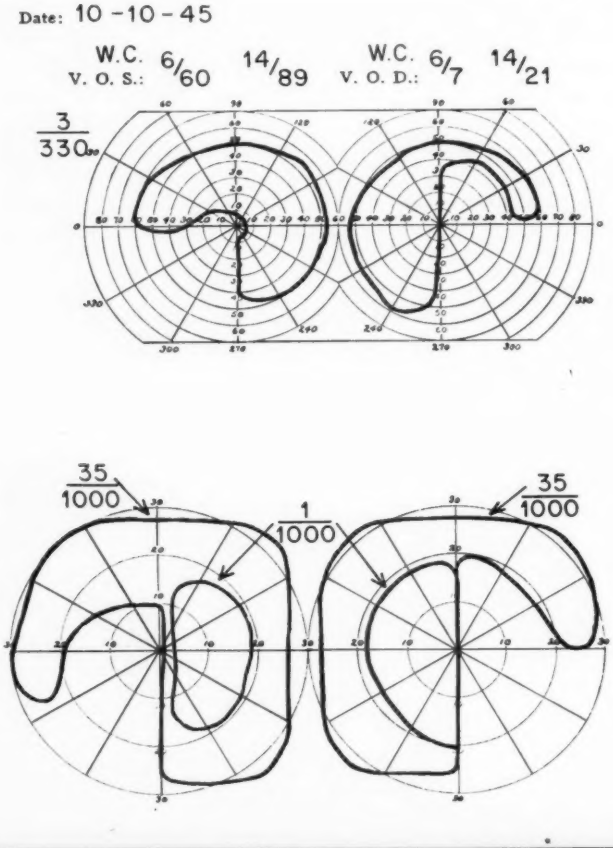


FIGURE 5. Visual fields revealing bitemporal hemianopsia with the greatest loss in the lower quadrants. There was also loss of central vision in the left eye. The initial complaint of diabetes insipidus preceded the visual-field loss by almost a year. The x-ray appearance of the head was normal.

bitemporal defects of the visual fields developed, the presence of a pituitary tumor was no longer in doubt.

As mentioned under question 1, the only clinical sign of insufficiency of the neurohypophysis is diabetes insipidus. Such cases are frequently labeled "idiopathic," when no obvious cause can be found. However, in such instances every effort should be made to determine the etiology of the neurohypophyseal insufficiency. Roentgenograms of the head and an examination of the visual fields should be carried out in every case to rule out a tumor of the sellar region. Efforts to diagnose systemic diseases such as xanthomatosis and sarcoidosis should be made. Should such efforts be of no avail the patient should be kept under observation, as is illustrated by the following:

Case 3—A 32 year old man was first seen at the Mayo Clinic in 1945 with the complaint of excessive thirst and urination for six months as well as occasional headaches. He stated that he drank about a pint of water every hour. On examination nothing abnormal was found. The specific gravity of the urine was 1.005. X-ray examination of the head gave normal results. A gross visual-field examination done in the Section of Ophthalmology also gave normal results. Consequently the patient was given nasal insufflations of posterior pituitary powder which adequately controlled his diabetes insipidus.

The patient returned six months later complaining of severe headache and decreasing vision. There was no clinical evidence of anterior pituitary insufficiency. The x-ray appearance of the head was again normal, but study of his visual fields by tangent screen and perimeter revealed partial bitemporal hemianopsia with the greatest loss in the lower quadrants. There was also loss of central vision in the left eye (figure 5). Examination of the optic nerves revealed a suggestion of pallor of both optic disks.

Because of the defects in the visual fields and the diabetes insipidus, a left transfrontal craniotomy was done, revealing a craniopharyngioma in the region of the sella turcica.

In this case diabetes insipidus was the first evidence of disease in the sellar region. Later, bitemporal hemianopsia combined with the initial posterior pituitary (neurohypophyseal) failure was sufficient evidence of a pituitary tumor to warrant an operation.

In such cases as this, in which only the neurohypophysis is involved initially, the tumor may later increase in size and destroy the anterior pituitary lobe. If anterior pituitary failure develops in a patient with diabetes insipidus, the polyuria may undergo partial or total remission. This is thought to be the result of the general lowering of the metabolism of the body as the gonads, thyroid and adrenals fail. Such amelioration of diabetes insipidus should alert the clinician to look for evidence of anterior pituitary insufficiency rather than reassure him that the disease process causing the diabetes insipidus is regressing. A case illustrating this was reported by us previously.[5]

Summary

Pituitary insufficiency, whether anterior, posterior or both, indicates disease in the region of the sella turcica and hypothalamus. Among the various causes of pituitary insufficiency are tumors of this region. Consequently, not infrequently the first clue the clinician may find suggesting a pituitary tumor is pituitary insufficiency. Even single findings such as amenorrhea or diabetes insipidus should alert the clinician to the possibility, even though remote in the instance of amenorrhea, that a pituitary tumor may be present. In such instances the diagnosis of a tumor will usually await additional evidence such as visual-field or x-ray changes.

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Diabetes is far more difficult to control in young patients than in older patients. The inefficiency of carbohydrate homeostasis in juvenile diabetes necessitates a regimen of close observation and regulation. The patient's caloric needs should be evaluated at six month intervals or less. The desired degree of control determines the type of insulin used and the administration. A psychosomatic approach also is essential for proper management. Young diabetic patients should consider their condition an inconvenience, not a disability.

Management of the Adolescent Diabetic Patient

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In recent years there has been an ever-increasing number of young persons in the diabetic population. A better understanding of diabetic management, plus the availability of efficient adjunct therapy, has brought about a prolongation of the life of juvenile diabetics, which was not seen 25 years ago. It is the purpose of this paper to consider some aspects of management of the adolescent diabetic patient.

The term adolescence will be used to designate the period of life ranging from puberty to the age of 20 years. Diabetes developing during this period, or prior to it, will be termed broadly juvenile diabetes, although some authors use this term only to designate diabetes that develops at the age of 15 years or less.

When a physician is confronted with an adolescent diabetic, he must manage a patient who is afflicted with a very unstable carbohydrate metabolism. Diabetes is far more difficult to control in young patients than it is in older patients. There is a wide fluctuation in the concentration of blood glucose, and ketosis can occur rapidly. Relatively small changes in the dose of insulin can cause rapid changes in the concentration of blood glucose. Decrements of as little as 5 units may be sufficient to produce symptoms of hyperglycemia or even ketosis.

Frequently, with the onset of hyperglycemia, the young diabetic will notice dryness of the mouth, sudden fatigue, or drowsiness which appears before significant glycosuria develops to cause symptomatic polyuria. Consequently, he can often tell when hyperglycemia is present without testing his urine. Of particular importance is the marked degree of hypoglycemia that occasionally may occur when only a small excess of insulin is administered. Not

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TABLE 1

DAILY CALORIC REQUIREMENTS OF ADOLESCENT DIABETIC BOYS AND GIRLS*

AGE, YR.	MEAN WEIGHT, LB.		CALORIES PER DAY		CALORIES PER POUND	
	Boys	*Girls*	*Boys*	*Girls*	*Boys*	*Girls*
11	84.5	82.5	2383	2156	27.7	26.7
12	93.0	90.2	2436	2246	26.6	24.4
13	101.2	101.6	2599	2241	25.6	22.3
14	112.8	111.8	2763	2177	24.1	20.2
15	125.4	117.5	2930	2074	23.7	18.2
16	135.2	124.4	3029	2097	22.6	17.5
17	142.8	130.4	2977	2133	21.0	16.5
18	154.4	132.4	2989	2020	20.3	15.3

*As reported by Wilkins, Ruby, Kelly and Jackson.[2]

only may the concentration of blood glucose decrease to a very low level, but there often is a delay in the compensatory output of glucose by the liver, and the concentration of blood glucose may remain low for a long period. For example, when 7 units of insulin is administered intravenously to a normal person, it will cause a decrease of approximately 50 per cent in the concentration of blood glucose, but the concentration will return to normal in an hour. However, if the maintenance dose of insulin is increased by 5 units in a case of juvenile diabetes, it may cause prolonged hypoglycemia even when it is administered subcutaneously.

In cases of juvenile diabetes, the inefficiency of carbohydrate homeostasis necessitates a regimen of close observation and regulation. Controlled eating habits are essential for the comfort of the patient and for the control of the unstable diabetes. Even physicians who prescribe unmeasured diets stress the need for good eating habits and certainly do not condone the use of excessive amounts of sweets or carbohydrates.

Table 1 shows the average number of daily calories prescribed for adolescent diabetics at the Diabetic Clinic of the College of Medicine of the State University of Iowa. There will, of course, be considerable variation on either side of the average, depending on the size and activity of the patient. One should note that the number of calories per pound of body weight are decreased after the cessation of growth. A common mistake is the prescription of insufficient calories for the growing, active teen-ager. In most cases, it is necessary to prescribe midafternoon and bedtime feedings, especially if the patient exercises at school. In the planning of the diet, the meal plan and exchange lists of the American Dietetic Association and the American Diabetes Association are very useful.*

It is advisable to evaluate the patient's caloric needs at intervals of six months or less during the adolescent period. The young patient will soon complain if he is not getting enough to eat. If his diet is not increased when indicated, he may refuse to follow any dietary regimen. An inadequate diet usually leads to irregular eating habits and to a gross lack of control.

The type of insulin used and the timing of its administration will be determined by the degree of control desired. If the maintenance of the concentration of blood glucose at a normal level is the desired goal, the method proposed by McArthur and Jackson[1] appears to be most suitable. When this method is used, a mixture of NPH insulin or globin zinc insulin and regular insulin is given before breakfast, and NPH insulin or globin zinc insulin is given alone before supper. The total daily dose is distributed so that the patient receives before breakfast a mixture of intermediate-acting and quick-acting insulin amounting to

*Copies of these lists may be purchased from the American Dietetic Association, 620 North Michigan Avenue, Chicago 11, Illinois, or from the American Diabetes Association, Inc., 1 East 45th Street, New York 17, New York.

approximately 50 per cent and 15 per cent, respectively, of the total daily dose, and the remaining portion of the dose is administered as an intermediate-acting insulin before supper. For example, a patient who needs 60 units of insulin a day would receive before breakfast a mixture of 30 units of NPH insulin and 10 units of regular insulin, and before supper he would receive 20 units of NPH insulin.

Other authors have believed that a single daily injection of a mixture of protamine zinc insulin or an intermediate-acting insulin with varying amounts of regular insulin or crystalline zinc insulin will suffice. When this method is used, the most satisfactory mixture consists of approximately five parts of NPH insulin to one part of regular insulin or approximately one part of protamine zinc insulin to two parts of regular insulin. On the other hand, physicians who condone asymptomatic glycosuria have found that the use of an intermediate-acting insulin alone is satisfactory. It is likely that mixtures of the new lente insulins eventually will answer all needs.

There is increasing use of the lente insulins. These products are more refined than those mentioned previously and currently are available in three preparations: semilente, a rapid-acting type; novolente, usually referred to as lente, which has a timing similar to that of NPH insulin and globin zinc insulin; and ultralente, which has a longer time of action than protamine zinc insulin. Novolente and regular or crystalline insulin may be mixed in a five to one ratio. However, mixing and injection must be carried out rapidly or attenuation of strength may occur. It is possible that, in the future, combinations of the lente insulins will suffice for most needs.

The orally administered hypoglycemic agents developed to date have not proved to be satisfactory substitutes for insulin in treating juvenile diabetes. The sulfonylureas, tolbutamide (ORINASE®) and chlorpropamide (DIABINESE®), have no effect in the young diabetic except possibly at the very onset of his disorder. The preparation known as DBI (N-beta-phenethylformamidinyliminourea) appears to have some effect in juvenile diabetics. Recent studies suggest that it may act as an adjunct to insulin and help stabilize the particularly "brittle" patient. However, there is a high incidence of side effects.

Use of the qualitative urinary sugar determination is the simplest means of judging control over a period of time. When possible, it is probably best to conduct tests before meals and at bedtime. A record should be kept of these tests, as it will enable both the patient and the physician to evaluate progress. The most popular means of testing is by copper reduction with CLINITEST® tablets. It is hoped that simple paper strip methods will soon be available. In my experience it is difficult to utilize single blood sugar determinations as a guide to control, since in the active teen-ager the concentrations may vary rapidly between high and low levels. Nevertheless, some authorities on juvenile diabetes recommend that frequent blood sugar determinations be made and that the concentrations be kept under 200 mg. per cent. Although this state may be attained in the hospital, it may be quite difficult to obtain it in the home. Many teen-age diabetics simply cannot achieve this degree of control and aglycosuria without experiencing frequent hypoglycemic episodes. The best control that I have been able to obtain in the active young patient is an average of two urines free of sugar daily.

Ketosis is closely linked to a fluctuation in the concentration of blood glucose. In cases of adolescent or juvenile diabetes, mild ketosis may develop rapidly during starvation, following hyperinsulinism, during emotional or physical stress, in the course of infections, or without any demonstrable associated condition. In any event, ketosis should be considered deleterious, not only because it may herald the development of acidosis, but also because it signifies disordered carbohydrate metabolism and a negative nitrogen balance. It has been said that hypoglycemic ketosis occasionally may be severe enough to produce acidosis. Chronic mild ketosis may be a clue to the presence of a hidden infection. Undoubtedly, many different factors act alone or in combination to produce ketosis rapidly in cases of juvenile diabetes.

TABLE 2

MILD KETOSIS ACCOMPANYING PHARYNGITIS*

TIME	URINALYSIS	INSULIN	REMARKS
9 A.M.	Glucose grade 4; acetone strongly positive	12 units of regular insulin	Patient ate breakfast and took an additional 250 cc. of orange juice
11 A.M.	Glucose grade 4; trace of acetone	6 units of regular insulin	Patient ate lunch
12 noon	Glucose grade 4; acetone negative		
5 P.M.	Glucose grade 2; acetone negative		Patient ate supper

*The patient was a 14 year old girl who was treated at home and who was taking 60 units of NPH insulin in the morning. Neither polyuria nor nausea was present.

TABLE 3

KETOSIS ASSOCIATED WITH MILD ACIDOSIS*

TIME	URINALYSIS	INSULIN	REMARKS
10 A.M.	Glucose grade 4; acetone strongly positive	25 units of regular insulin	Anorexia and thirst
11 A.M.	Glucose grade 4; acetone strongly positive	25 units of regular insulin	Anorexia and thirst
12 noon	Glucose grade 4; acetone moderately positive	25 units of regular insulin	Anorexia
1 P.M.	Glucose grade 4; trace of acetone	None	Asymptomatic
2 P.M.	Glucose grade 4; acetone negative	None	
3 P.M.	Glucose grade 2; acetone negative	None	
5 P.M.	Glucose grade 2; acetone negative	None	
7 P.M.	Glucose grade 1; acetone negative	None	

*The patient was an 18 year old boy who was taking 75 units of NPH insulin. No cause for the ketosis could be found. Polyuria and mild thirst were present. The patient was alert but anorexic. He had taken 75 units of NPH insulin on the morning of the attack, and he had eaten a light breakfast. The value for the blood glucose was 385 mg. per 100 cc., and the carbon dioxide-combining power of the plasma was 18 mEq. per liter.

Mild ketosis that occurs without acidosis and follows hyperinsulinism will abate after the administration of carbohydrate. Sporadic ketosis that occurs during fasting is common and usually is without significance. However, if it continues, adjusting the diet by administering carbohydrate at bedtime may eliminate it, especially if the urine is free of sugar while the patient is fasting and if the concentration of blood glucose is low. Ketosis occasionally may occur during the day without causing any symptoms. This also may be without significance, since urinalysis may fail to reveal any evidence of ketosis two hours later. However, if infection is present, or if asymptomatic ketosis continues to occur intermittently, it may be necessary to use small increments of quick-acting insulin, preferably with added carbohydrate. For example, 5 to 10 units may suffice if the patient has been taking 40 to 60 units a day, and 10 to 20 units may be sufficient if the patient has been taking more than 100 units a day. Increased doses of insulin must be prescribed judiciously in cases of juvenile diabetes, since slight overdosage may cause hypoglycemia. If ketosis occurs persistently and causes symptoms, or if it is associated with infection, larger amounts of quick-acting insulin and carbohydrate may be necessary.

Tables 2 and 3 include the clinical data in two cases of ketosis in which supplemental insulin was required. In all cases of juvenile diabetes, a urinary test for acetone, such as ACE-

TEST® reagent tablets or the DENCO® acetone test, should be available in the patient's home. If the patient and his family are intelligent, episodes of mild ketosis can be adequately managed at home. The physician can keep in touch with his patient by telephone. It is a drain on hospital beds to admit all young diabetics with mild ketosis, and frequent hospitalization is deleterious to the patient's mental health. The patient also learns more about the treatment of the ketosis when the treatment is administered at home. Knowledge gained in this way will help the patient to prevent acidosis if ketosis develops and medical consultation is not immediately available.

Ketosis and acidosis are considerably more frequent in cases of adolescent diabetes than they are in cases in which the patients are older. Ketonemia associated with a decrease in the carbon dioxide-combining power of the plasma to less than 20 mEq. per liter may occur in 6 to 10 hours after an apparently normal state. Moreover, ketosis and acidosis may develop before significant hyperglycemia occurs, and there may be an absence of polyuria or thirst. This course of events is in contrast to that which occurs in older diabetics who are resistant to insulin and who experience the classic symptoms of developing acidosis for 24 to 48 hours.

The principles of therapy of acidosis in young diabetics are similar to those in cases in which the patients are older. However, certain aspects are worthy of comment. First, since the concentration of blood glucose may not be unduly increased when the patient is admitted to the hospital, it may be wise to administer a 5 per cent solution of glucose in physiologic saline solution from the beginning of treatment in a case of mild acidosis. Physiologic saline solution can be used alone if it is found that the concentration of blood glucose initially exceeds 500 mg. per 100 cc. Otherwise, hypoglycemia may easily develop if sufficient glucose is not administered in a case of acute, mild ketosis and acidosis. Second, the sensorium of a young diabetic usually will clear more rapidly than that of an older diabetic, and fluids may be given orally earlier. Third, severe potassium deficiency may occur in juvenile diabetics as in older diabetics. Although this does not occur in all cases, its seriousness warrants constant observation for its development. It should be emphasized that diabetic acidosis is one complication that is preventable and reversible. There is little excuse for its development if the patient is managed well.

Hypoglycemia is an ever-present problem in cases of juvenile diabetes. Because juvenile diabetics are sensitive to insulin, they are prone to undergo more severe and more prolonged episodes of hypoglycemia than are older diabetics who are resistant to insulin. Irreversible cortical damage and idiocy have been reported to have occurred in young diabetics. A review of the cases in which these changes have occurred would seem to correlate the changes with the duration of the hypoglycemia.

All juvenile diabetics should carry some form of carbohydrate as a preventive measure. In particular, exercise is likely to precipitate an insulin reaction. The center on the basketball team of a local high school, who was taking 160 units of NPH insulin a day, found that he could prevent an insulin reaction during a game only if he ate a candy bar 30 minutes before the game and if he ate an orange at the start of the game and between the halves. Finally, insulin reactions are a genuine source of embarrassment, especially when the young patient may be ridiculed by his friends.

Although tuberculosis and pyelonephritis often occur in the diabetic, they may be looked for particularly in the younger patient. Fortunately, chemotherapy has aided greatly in the treatment of tuberculosis. However, pyelonephritis continues to rank as one of the most serious complications of diabetes. Workers at the Joslin Clinic have shown that uremia is the most common cause of death of the juvenile diabetic and that pyelonephritis is a major causative factor in the uremia. Repeated examinations should be made to detect the development of these two infections. If cystitis is found, it should be treated vigorously, and the urine should be examined frequently for evidence of latent infection.

In the growth and development of the juve-

TABLE 4

TOTAL INCIDENCE OF VASCULAR LESIONS ACCORDING TO DURATION OF DIABETES*

DURATION OF DIABETES, YR.	INCIDENCE OF VASCULAR LESIONS, PER CENT				
	Albuminuria	*Increased blood pressure*	*Retinitis*	*Retinitis proliferans*	*Calcification of arteries*
0 to 4	0.8	0.5	0	0	0
5 to 9	1.5	1.2	2.5	0	1.7
10 to 14	7	4.5	19	3	14
15 to 19	18	15	59	18	44
20 to 24	41	32	82	47	73
25 to 29	39	44	88	46	88
30 to 34	44	53	93	59	94
35 to 39	63	70			

*As reported by White.[3]

nile diabetic, two events are worthy of comment. In the past, retardation of growth was observed commonly. The combination of dwarfism, hepatomegaly and insulin sensitivity was designated as the Mauriac syndrome. It now is generally believed that poor control of the diabetes during the critical period of growth was responsible for the decreased growth. With current standards of control and nutrition, the growth of juvenile diabetics usually is normal.

The second problem in development concerns occasional delays in the development of puberty in both sexes. In girls, the menarche may be delayed, especially if the diabetes develops before they are 11 years old. Irregular menstruation is a frequent complaint. Despite this, there is no evidence of decreased fertility in the diabetic woman of childbearing age.

It is beyond the scope of this presentation to consider in detail the degenerative complications of juvenile diabetes. The development of retinopathy and nephropathy in the young diabetic is one of the most distressing situations in clinical medicine. Fortunately, these complications usually are not observed during adolescence unless the disease developed before the patient was 10 years old and has been present for approximately 15 years. Table 4 shows the incidence of vascular lesions according to the duration of juvenile diabetes in a group of cases reported by White.[3] There was a rapid increase in the incidence of retinopathy after the disease had been present for 15 years. This is indeed discouraging in view of the good care received by the patients. Neuropathy is unusual in adolescence and occurs later in the course of the diabetes.

Authors do not agree as to whether the early occurrence of degenerative complications is due to poor control of the diabetes. Currently, most authors believe that an attempt should be made to control the diabetes. Consequently, it would seem advisable to maintain as normal a physiologic state as is practical until the issue is settled. However, it does not seem logical to carry control to the point where maintenance of aglycosuria necessitates a life of reactions and curtailed activity.

If there ever was a disorder in which a good psychosomatic approach is essential for proper management, it is juvenile diabetes. There are few diseases wherein the physician must know and understand all aspects of his patient as well as in juvenile diabetes. The announcement of the diagnosis is startling to the patient, and especially to his relatives. The presence of a bewildering disorder may make the average teen-ager rebellious, not only to medical advice but to his parents as well, for he is being forced to do things which for him are abnormal and unnecessary.

Successful treatment requires that the patient have confidence in his physician and that he be willing to follow his advice. Perhaps the first step in obtaining the patient's cooperation is that the physician develop in himself a sincere interest in his patient's welfare. Without this, counseling becomes cold, and is a drudgery. If the patient realizes that the physician is interested in him as a person as well as in his disease, he will tend to pay greater heed to management. The patient must be constantly reassured that he can lead a normal life if he will cooperate with his physician. For example, many teen-age girls fear that they never can raise a family. The boys want to know if they can continue with athletics. The diabetes should be considered an inconvenience, not a disability.

With kindness and encouragement, it often is possible to convert an uncooperative patient. Pampering or permitting laxity of control occasionally is necessary to maintain some degree of rapport with the patient. Otherwise, the patient may refuse all medical advice and may be in dire straits of acidosis or infection when he is seen again. It sometimes is necessary to make the patient dependent. However, although this type of patient may consult his physician about all matters, he usually will not follow any prescribed regimen satisfactorily. If all measures fail or serve to drive the patient further away, it may be that the physician can only state that he will always be available if needed. The patience of the physician may be taxed almost to the limit by the recalcitrant young diabetic.

Occasionally, a family that has some knowledge of diabetes will want to know about the ultimate prognosis for their child. At present, the life expectancy of the juvenile diabetic is limited. In the large group of cases of juvenile diabetes reported by White,[3] few of the patients lived for more than 35 years after the development of the diabetes. However, a brighter outlook can be held for young persons in whom diabetes is developing at present, since in the future it is likely that not only will adjunct therapy be further improved, but there should be better knowledge of the mechanism of production of the degenerative vascular processes. Accordingly, it is plausible to err on the side of optimism in that when the time comes to expect complications the picture may be entirely different from what it is today.

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Fractures and Fracture-Dislocations of the Ankle

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Accurate diagnosis and proper choice of treatment in fractures and fracture-dislocations of the ankle require a knowledge of the mechanisms of injury.

Good x-rays, centered over the joint in true anteroposterior and lateral projections, are also prerequisites to accurate diagnosis.

Closed methods of treatment may be used in many cases, but certain fractures require open reduction. Surgery must be precise, and, to allow the indicated correction to be made, x-rays should be taken in the operating room before the wound is closed.

MANY fractures and fracture-dislocations of the ankle can and should be treated by closed methods. However, in order to obtain good anatomic and functional restoration in certain fractures, open reduction may be required. In cases in which it may be used, internal fixation has the advantages of a shorter healing time, less immobilization in both time and degree, and faster return to normal activities.[1]

Accurate diagnosis and proper choice of treatment of these injuries require a knowledge of the mechanisms of injury and the classification of injury based on these mechanisms. Good x-rays, centered over the joint in true anteroposterior and lateral projections, are prerequisites to accurate diagnosis. More information is obtained from an x-ray taken with the ankle in 20 degrees of internal rotation. This neutralizes the normal external torsion of the ankle and gives a true anteroposterior view. If open reduction is the method of choice, the surgery must be precise; x-rays taken before the wound is closed are necessary to assure precision reduction and to allow indicated correction to be made.

History and Classification

Percival Pott first described the abduction mechanism of injury to the ankle in 1775. Boyer added the mechanism of adduction in 1803. His pupil Dupuytren first produced these fractures in cadavers. By 1840 Maisonneuve added the third mechanism—external

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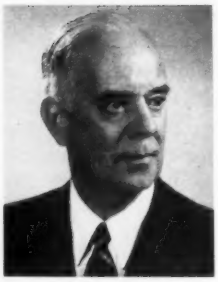

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rotation—which he discovered while producing fractures experimentally in cadavers. He correctly believed this to be the most common mechanism of injury.

With the advent of x-ray, the experimental approach was abandoned, and there followed a series of classifications of ankle injuries—some anatomic, some purely descriptive—all ignoring the observations of the earlier students. In 1922 Ashurst and Bromer,[2] in the first truly modern paper on ankle injuries, classified all of their cases on the basis of mechanism of injury.

It is believed that the severity of injury and the therapeutic requirements are better understood if fractures and fracture-dislocations of the ankle are thought of as one or another degree of the four basic mechanisms of injury. A thorough knowledge of the structures injured, ligamentous as well as bony, leads to more accurate treatment. In an excellent monograph, Bonnin[3] analyzed in detail all aspects of fractures of the ankle.

Adduction injuries—When the foot is forcibly adducted or inverted (figure 1), the most minor injury that can occur is sprain of the lateral ligaments. These ligaments may be completely torn if the force continues. Instead of rupturing, the ligament may avulse a small or a large fragment of the lateral malleolus. This is the first degree of adduction injury. When medial talar shift predominates over talus varus, the alternate first-degree injury may occur, namely, a vertical fracture of the medial malleolus. It is vertical because it is sheared off by the talus. If the inverting force continues, a combination of these fractures occurs, producing a second-degree adduction, bimalleolar fracture. The alternate injury would be rupture of the lateral ligaments with a vertical fracture of the medial malleolus, although this injury is uncommon. We have had a recent case of this rare injury.

There may be a good deal of forward momentum of the tibia on the talus in these injuries; as the force continues, the posterior tibial lip of the tibia is sheared off, producing the third-degree injury with posterior medial dislocation. This is the uncommon type of trimalleolar fracture.

External rotation injuries—External rotation of the foot on the leg (figure 2) first causes either a rupture of the anterior tibiofibular ligament (a common type of ankle sprain) or a spiral oblique fracture of the lateral malleolus. It is oblique because of the lateral shearing force and spiral due to the torsional force. In the cases in which the fracture is above the level of the joint, the anterior tibiofibular ligament ruptures prior to the fracture of the fibula. As the force in external rotation continues, the medial malleolus is avulsed, giving a slightly oblique fracture line. Alternately, the deltoid ligament may rupture. Either of these injuries constitutes the second-degree, external rotation injury. The tear of the deltoid ligament and the avulsion of the medial malleolus occur with equal frequency; pure chance determines which of these injuries occurs in any given case.

One of our problems is to differentiate the first-degree injury and the second-degree injury with tear of the deltoid ligament, since these injuries may give identical x-ray appearance. Simply allowing the foot to fall into external rotation will show on x-ray a widening of the medial joint space if there is partial or complete rupture of the deltoid ligament. These two injuries require quite different treatment. The first-degree injury with oblique fibular fracture requires simply that a short leg walking cast be worn for six weeks. In a second-degree injury with rupture of the deltoid ligament, a long leg cast must be worn for six weeks, preferably followed by wearing of a short leg walking cast for a month. Treating this injury with a short cast will

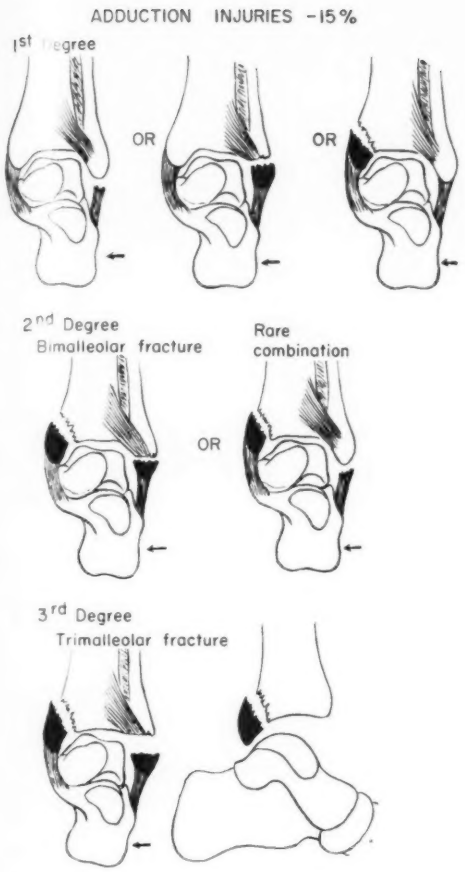


FIGURE 1.

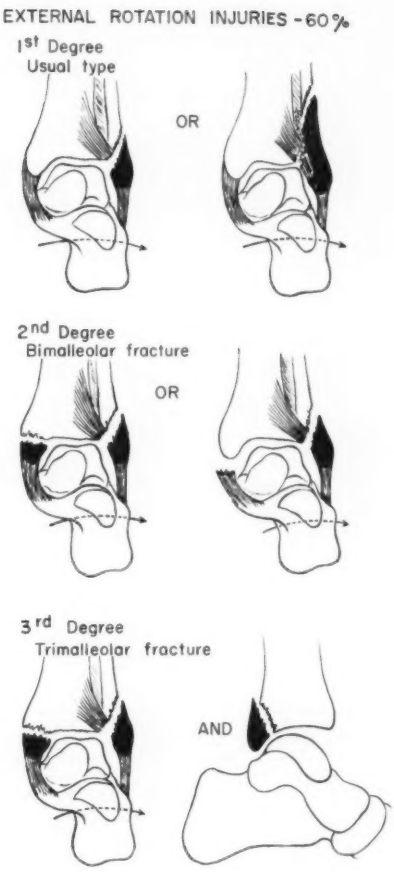


FIGURE 2.

sometimes result in a widened ankle mortise and permanent impairment of the joint.

If the force of external rotation continues, the posterior lip of the tibia is avulsed or sheared off, and the talus dislocates posteriorly. This is the third-degree injury, the common type of trimalleolar fracture.

Abduction injuries—The classic example of the abduction injury (figure 3) is the situation in which a leg is struck from the lateral side by a log rolling down a hill. This produces a pure abduction force of the foot on the ankle. The first-degree injury is avulsion of the medial malleolus as a transverse fragment or its alternate, rupture of the deltoid ligament. This latter diagnosis is made only by the astute clinician who takes an abduction stress x-ray after injecting the medial side of the ankle with NOVOCAIN®. As the force in abduction continues, one of two things may happen: (1) The tibiofibular ligaments may hold, and the lateral malleolus is then sheared off obliquely at the joint line but without a spiral element (this fracture will be below the level of the tibiofibular ligaments), or (2) the tibiofibular ligaments may rupture, giving a complete tibiofibular diastasis. A bending type of fracture of the fibula will then occur above the ligaments, usually about 3 in. above the tip of the malleolus.

It is most important to recognize tibiofibular diastasis, for severe disability can result

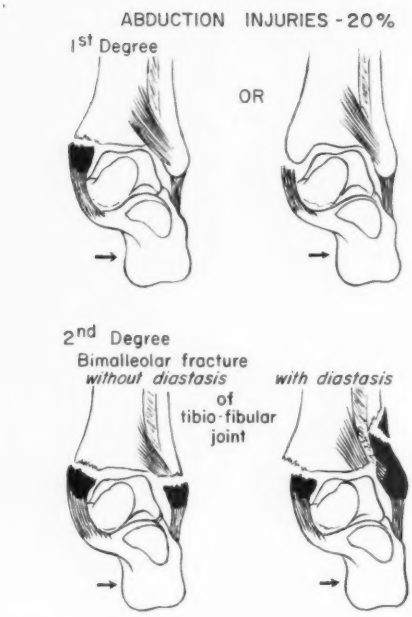
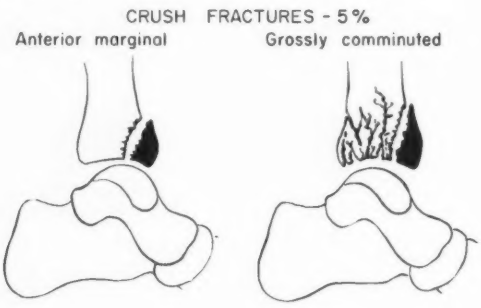


FIGURE 3.

FIGURE 4.



from allowing healing with a widened ankle mortise. It is a difficult fracture-dislocation to hold by plaster; open fixation of the joint will be required in a certain number of cases, especially when the deltoid ligament is torn. If the fracture is treated closed, the long leg plaster must be worn for eight weeks, followed by wearing of a short leg walking cast for four weeks. Frequent x-ray follow-up in the early weeks is strongly advised, since the ankle mortise all too often widens in the cast.

Crush fractures—Crush fractures (figure 4) occur from a fall or when the foot is forcibly hyperdorsiflexed. Anterior or posterior marginal fractures may occur in the minor degree of injury, but more commonly there is gross comminution of the distal tibia. Many types of fractures are encountered in the crush injury, depending on whether the crushing force is anterior or posterior, medial or lateral. Only an occasional case can be benefited by open reduction. Skeletal traction of the os calcis gives a good result in a number of cases, but either spontaneous or surgical fusion is the end result in many others.

Treatment

Closed reduction—In general, treatment should be instituted as soon as possible. The patient with an undisplaced fracture will be more comfortable in a padded cast than in a compression dressing for several days. If a case is seen late, however, and great swelling has taken place, elevation and a compression dressing are indicated.

Grossly displaced fracture-dislocations should be reduced immediately, even before x-rays are taken, for circulation in the foot and the viability of the skin over the sharp edges of the fractures are endangered. Final reduction and casting are then done with suitable anesthesia after proper preparation.

A first-degree injury will require only a short leg cast. A second-degree or third-degree injury will require a long leg cast with the knee bent 30 degrees. One must watch carefully for partial or complete rupture of the deltoid ligament, since in these cases a long leg cast must be worn to prevent displacement in external rotation (figure 5). It is wise to make an x-ray to check even the simple fractures of the lateral malleolus to be sure that widening of the ankle mortise has not taken place during application of the cast.

External rotation injuries are reduced by internally rotating the foot on the tibia, not by adduction or by putting the ankle in a varus position. The ankle should be immobilized at or near a right angle, with the foot in neutral position. If it is necessary to invert the foot and ankle to reduce the medial malleolus, open reduction is indicated. Long-term disability

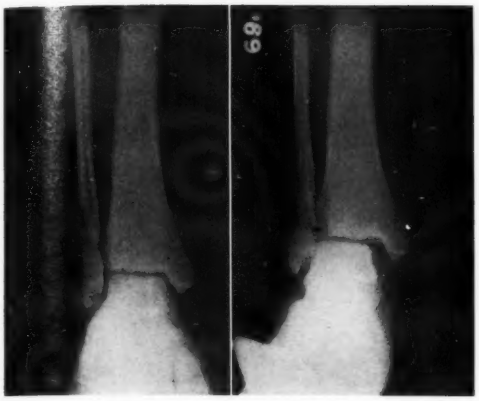


FIGURE 5. *Left.* X-ray showing what appears to be only a simple fracture of the fibula. *Right.* Allowing the foot to fall into external rotation reveals a partial tear of the deltoid ligament, evidenced by the widened medial joint space.

has resulted from immobilization in a deformed position, and this should be avoided at all costs.

A first-degree injury will require immobilization in plaster for six weeks; during most of this time, partial or even full weight may be borne in a short leg walking cast. Second-degree or third-degree injuries require a long cast for six weeks; this is best followed by a four week period in a short leg walking cast. Even if the fractures have healed, no time is lost in the walking cast, since rehabilitation following its removal is usually very rapid if the patient has walked a good deal in the cast. The incidence of reflex sympathetic dystrophy appears to be minimized by including a period in a walking cast.

Check x-rays are obtained early in the post-reduction period, so that if slipping takes place it can be corrected before healing occurs. In general, a typical trimalleolar fracture should be x-rayed, after the cast is applied, at five days, 10 days, six weeks and 10 weeks. Fractures in perfect position at 10 days are very unlikely to slip after that time if the cast fits well.

Elevation of the extremity during the first few days is very important to minimize pain and swelling; if this is done, splitting of the cast is rarely necessary. Ambulation on crutches is started as soon as swelling is controlled. Elevation of the extremity when the patient is sitting may be necessary throughout the immobilization period in some cases.

Open reduction of the medial malleolus—Indications—Failure to manipulate the medial malleolus into perfect position is the main indication for open reduction. Failure of accurate reposition is most often due to periosteal interposition at the fracture site. As the medial malleolus displaces, it usually pulls with it a flap of periosteum from the distal tibia; it is this material which often becomes interposed during reduction. The lateral x-ray will more often show separation of the malleolus than will the anteroposterior view (figure 6). Sometimes, the malleolus will be so locked in rotation that it is unreducible (figure 7). In a few cases the posterior tibial tendon has been interposed and has rendered the fracture unreducible. If a fracture is seen late, closed reduction will often be impossible and open reduction will be indicated (figure 8). In some adduction injuries in which there is a vertical fracture of the medial malleolus, there are often pieces of bone and cartilage which prevent reduction; surgery is indicated to remove these fragments (figure 9).

When it is necessary to hold the foot in a position other than neutral to reduce the fracture, open reduction is indicated. Severe problems in rehabilitation can result from immobilization in adduction or in varus position.

Open reduction of the medial malleolus is often indicated in abduction injuries with complete tibiofibular diastasis. Fixation of the malleolus may provide sufficient stability, so that further surgery may not be necessary.

Surgical technic—An anteromedial incision is made at the anterior border of the malleolus. Periosteal interposition is removed if present. The joint is inspected and irrigated, and fragments of bone and cartilage and clots are removed. The malleolus is then anatomically reduced, being held in position with a bone or towel clamp while a screw is placed. A slight increase in the anterior exposure allows the surgeon to inspect the joint and to verify the reduction. A small cruciate incision is made in the deltoid ligament, care being taken not

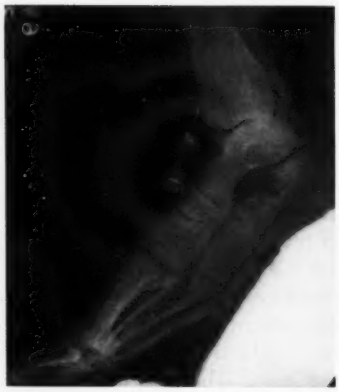


FIGURE 6. X-ray showing separation of the medial malleolus. This fracture can be better seen with a lateral view than with an anteroposterior view.

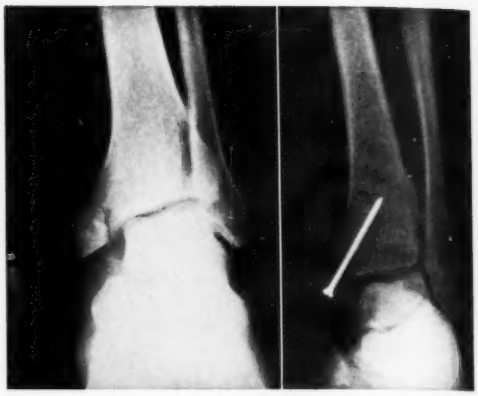


FIGURE 7. Unreducible, severely rotated medial malleolus. Union occurred in six weeks. The screw used in such fractures should be 2 in. long.

to strip any soft tissue unnecessarily from the fragment. A drill is then run in a superior lateral and posterior direction (since the medial malleolus is anterior), and a 2 in. screw is placed and buried under the deltoid ligament. X-rays in two planes are then taken to verify reduction of the talus and the medial malleolus as well as to check the position of the screw, which can very easily be placed too far laterally and will consequently be intra-articular (figure 10).

A screw shorter than 2 in. may not give enough fixation, and one longer than 2 in. must be placed either in a marked vertical position or through the lateral cortex of the tibia; neither of these maneuvers is necessary. A few cases have been seen in which the screw did not seat because the tip impinged against the lateral cortex. This holds the surfaces of the fracture apart and delays healing. The screw may exit from the anterior tibia if it is not moderately diverted posteriorly.

In the vertical fracture of the malleolus, it is often desirable to place the screw perpendicular to the fracture line. The larger the fragment, the more likely this is to be true (figure 11).

In general, when open reduction of the medial malleolus has been carried out, a long leg cast is not necessary. Six weeks of nonweight bearing in a short leg cast, followed by four weeks in a walking cast has been our routine procedure.

Repair of the deltoid ligament—In abduction and external rotation injuries, rupture of

FIGURE 8. Fracture seen two weeks after injury. Open reduction accomplished union in excellent position.

the deltoid ligament instead of the medial malleolus often occurs (figure 12). The rupture is most often of the anterior fibers only, and closed reduction usually is possible. Occasionally, however, the deltoid ligament will be interposed between the talus and the medial malleolus, preventing reduction of the talus. This is recognized by residual widening of the medial joint space on the postreduction x-ray (figure 13). In the few cases in which we have repaired the deltoid ligament, it has been found desirable to fix the site of the fracture of the lateral malleolus, so that no tension develops on the ligament while it is healing (figure 14). It is best to suture the ligament directly into bone through small drill holes to insure the repair. If the lateral malleolus has

FIGURE 9. In vertical fractures, the screw is often placed more horizontally. The loose fragments of bone in this case should have been removed.

FIGURE 10. *Left.* X-ray taken in operating room showing intra-articular placement of screw. *Right.* Replacement of the screw in the proper position.

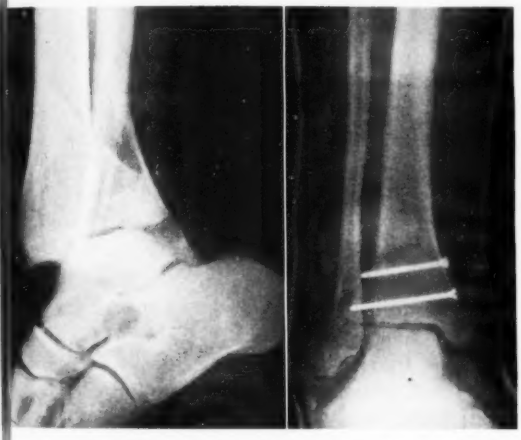


FIGURE 11. It is more desirable to place the screws horizontally in large fragments such as this one. This fracture was anatomically reduced by means of two screws.

FIGURE 12. Rupture of the deltoid ligament is a common alternative to fracture of the medial malleolus.

FIGURE 13. Residual widening of the medial joint space, indicating interposition of deltoid ligament.

been fixed, a long cast is not necessary. A month in a walking cast, after six weeks in a short cast, appears to be about the time that is required.

Open reduction of the posterior malleolus—In our opinion, open reduction of a fracture of the posterior tibial lip is not often indicated. In most cases, the fragment is small and does not involve the articular surface. It may appear to be large on the prereduction x-rays because it is flat and broad, but the postreduction views will show its true size. In these cases it is likely that the fracture is caused by avulsion by the posterior tibiofibular ligament. In other cases, however, the posterior fragment is split off by the talus as it rotates in the ankle mortise. The fragment may be large and involve a significant amount of the articular weight-bearing surface. Open reduction is indicated if the fragment consists of a third or more of the weight-bearing surface and if reduction is not excellent. A posterolateral approach is used, retracting the flexor hallucis longus with the neurovascular bundle. One or two screws afford excellent fixation. Check x-rays should be obtained to verify

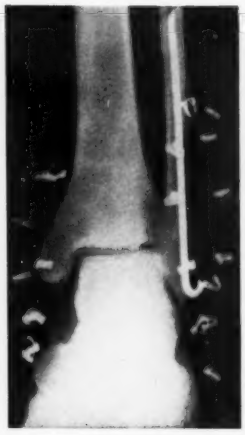


FIGURE 14. Following open repair of ligament, this fracture of the fibula was fixed with a Rush pin.

FIGURE 15. X-ray taken in operating room showing good reduction of the posterior malleolus and properly placed screw.

FIGURE 16. *Left and center.* Trimalleolar fracture of the external rotation type. *Right.* Postreduction x-ray.

FIGURE 17. Inversion x-ray of the ankle showing a torn calcaneofibular ligament.

FIGURE 18. Typical tibiofibular diastasis in which a perfect result was obtained by use of the Barr bolt.

anatomic restoration and position of the screws (figure 15).

Open reduction of the lateral malleolus—Open reduction of the lateral malleolus has never been widely favored by orthopedic surgeons, and the indications are not clear-cut as in the case of the medial malleolus. However, we cannot agree with the often-heard opinion that the position of the lateral malleolus is unimportant. One has only to consider the large articular facet with which nature has provided the lateral malleolus to realize the important role it plays in the function of the ankle joint.

Therefore, we insist on reasonably good reduction of the lateral malleolus and will do open reduction in some cases to achieve it. On occasion one will find a fragment of bone (usually from the lateral lip of the tibia, from which it has been avulsed by the anterior tibiofibular ligament) interposed at the site of the fracture and preventing reduction not only of the lateral malleolus but also of the talus. Interposition of the peroneal tendon has been occasionally seen.

Unless there is gross tibiofibular diastasis, it is not necessary to place a screw across the tibiofibular joint. We have found that intramedullary fixation is excellent. A Rush pin has been used, but a 4 in. screw gives better fixation (figure 16). When this is combined with internal fixation of the medial malleolus,

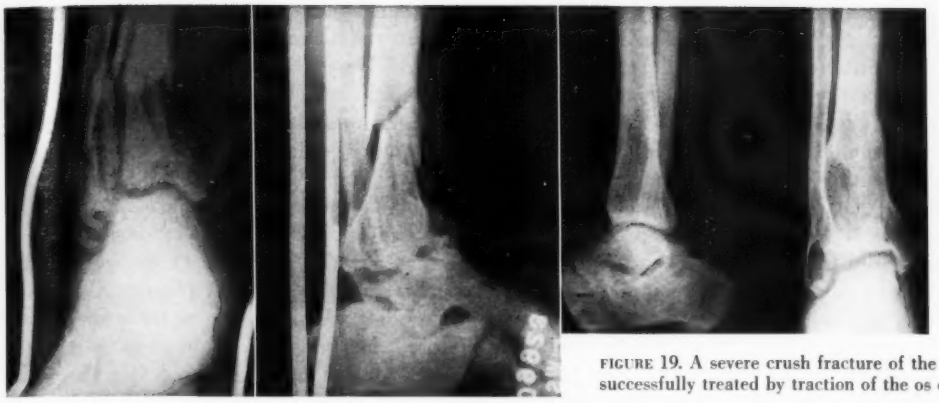


FIGURE 19. A severe crush fracture of the ankle successfully treated by traction of the os calcis.

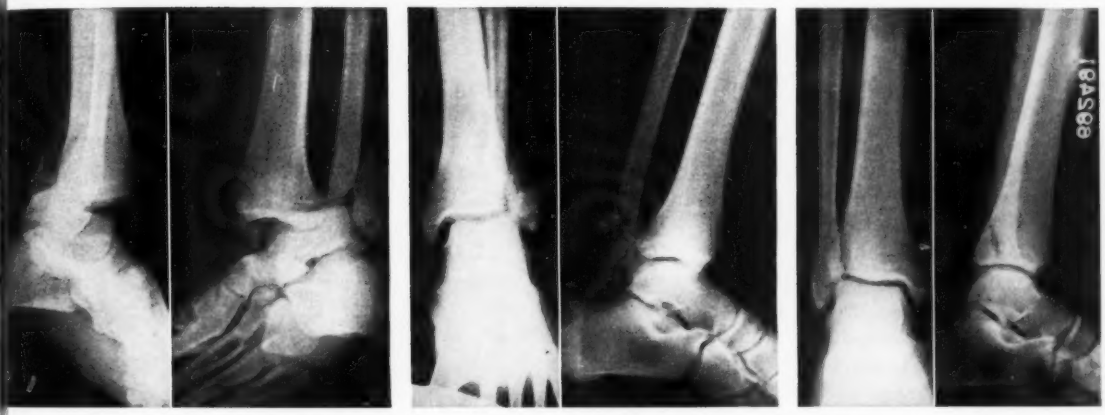


FIGURE 20. *Left.* Two views of a Bosworth fracture. *Center.* Views of the posterior and medial displacement of the proximal fibula after the initial reduction. *Right.* Views of the reduction after the second manipulation.

the amount and time of immobilization may be considerably reduced. After wound healing, a posterior mold can be used and can be removed daily for nonweight-bearing exercises. Walking can be resumed at six weeks. The screws need not be removed.

Repair of the calcaneofibular ligaments—It is our opinion that complete tears of the lateral ligaments of the ankle will respond well to immobilization in plaster and that open repair is not indicated. A short leg walking cast should be worn for eight weeks to insure sound healing.

It will be realized that the diagnosis will be made only by taking inversion x-rays of the anesthetized ankle. Tilting of the talus will be seen when the ligament is completely torn (figure 17). Some persons have congenital relaxation of the calcaneofibular ligament; therefore, x-rays of the uninjured side always should be taken for comparison.

Open reduction of the tibiofibular diastasis—When there is lateral displacement of the talus with a fracture of the fibula above the tibiofibular ligaments, diastasis of some degree is present. In external rotation injuries, the diastasis is usually incomplete; in abduction injuries, the diastasis may be complete, indicating that all parts of the tibiofibular ligament have been ruptured. These are the anterior tibiofibular, the posterior tibiofibular and the interosseous ligaments.

Closed reduction is usually possible, but the medial malleolus frequently will need open reduction. Perfect restoration of the medial joint space between the talus and the medial malleolus, indicating full reduction of the diastasis, must be accomplished.

Some of these injuries, however, are unstable and require internal fixation. This is more likely to be true when there is rupture of the deltoid ligament instead of avulsion of the medial malleolus. Rather than allowing the ankle to heal with any degree of widening, open reduction should be carried out (figure 18). A bolt or a wood screw is placed across the tibia and fibula close to the ankle joint. Higher insertion tends to angulate the lateral malleolus. An ordinary bone screw does not give sufficiently secure fixation. When the bolt or screw is tightened, the ankle must be held at right angles, at which time the wider anterior part of the talus is in the mortise. If the bolt is tightened over the narrow posterior foot of the talus, restoration of dorsiflexion may be impossible.

The internal fixation must be removed before weight bearing is begun, usually at six weeks. This is done to restore the normal opening and closing function of the tibiofibular joint during weight bearing. The stress of weight bearing probably would cause a retained screw or bolt to break.

Open reduction of crush fractures—In occasional isolated anterior fractures, open reduction may be indicated to restore normal anatomy. In the majority of cases, however, the distal tibia is shattered beyond surgical repair. Treatment is by traction through the os calcis for a month, followed by immobilization in plaster for two months (figure 19). Some fractures will respond well to this treatment, but others will require arthrodesis of the ankle.

Open reduction of the Bosworth fracture—In 1947 David Bosworth[4] described a group of cases in which the proximal fragment of the fibula was displaced behind the tibia. All of his cases, seen late, required open reduction. At surgery it was necessary to lever the proximal fibula with considerable force. We have had two of these cases;[5] however, they were seen early, and in both we reduced the fractures by closed means (figure 20).

The displacement must be recognized early before it becomes fixed. Considerable manipulation force is necessary to bring the fibula anteriorly and laterally.

Conclusions

1. An understanding of the mechanisms of injury in ankle fractures is necessary in order to obtain the best therapeutic results.
2. Surgery for ankle fractures is indicated under certain circumstances.
3. Reduction should be precise and verified by x-rays taken in the operating room.
4. Anatomic reduction is the goal to be achieved and will insure the highest percentage of satisfactory results.

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Recognition and Management of Allergy in the Preschool Child

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Allergy was established as a cause for symptoms in 90 per cent of 182 preschool children referred to an allergy clinic. Allergic rhinitis and asthma were the most common conditions. The typical history, physical and laboratory findings are presented. Therapy should include removal of the causative agent and desensitization of the child rather than symptomatic measures. Types of medication are discussed, and the author emphasizes that steroids should be used only for major allergic crises.

EARLY recognition of allergy and allergic tendencies in the preschool child may be a decisive factor in determining his health pattern throughout his life. The correct diagnosis of allergy may prevent much fruitless treatment, overprotection, invalidism and irreversible changes that are produced by the allergy itself.

SUSAN C. DEES

In order to summarize some features of allergy in children of preschool age, we reviewed the records of 182 children from two to six years of age who were seen for the first time in our allergy clinic during 1957. In our series, boys slightly outnumber girls at every age, with an over-all ratio of four boys to three girls. The group of five to six year old children, composed of 57 patients, was slightly larger than the three younger age groups, which included between 40 and 43 patients (table 1).

Allergic rhinitis and asthma were the two conditions encountered most frequently (table 2). Allergic rhinitis was present in 111 children and was suspected in five children. Asthma was established as a diagnosis in 107 children and was suspected in 23 children.

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TABLE 1

AGE AND SEX OF 182 ALLERGIC CHILDREN

AGE (Years)	BOYS	GIRLS	TOTAL
2 to 3	25	17	42
3 to 4	22	21	43
4 to 5	22	18	40
5 to 6	35	22	57
TOTAL	104	78	182

TABLE 2

DIAGNOSES* OF ALLERGIC CONDITIONS IN 182 PRESCHOOL CHILDREN

CONDITION	NUMBER OF CHILDREN	
	Condition present	*Condition suspected*
Allergic rhinitis	111	5
Asthma	107	23
Eczema	34	1
Urticaria	4	
Conjunctivitis	3	
Gastrointestinal allergy	2	

*Multiple diagnoses per patient.

At this age eczema is beginning to decline in importance, as shown by only 34 children with this condition. In 10 of these children, a congenitally dry skin, ichthyosis of varying degree, dyshidrosis or some more marked disturbance of sweating was actually of as much or of more significance than the eczema in causing symptoms.

Since the presenting complaint in the preschool child frequently was "keeping a cold," the question of tonsillectomy and adenoidectomy was raised repeatedly. Six children had had adenoidectomy and eight had had tonsillectomy and adenoidectomy before referral. We recommended operation for 19 children in whom we found recurring infection and enlarged tonsils and adenoids. Five of these children subsequently had adenoidectomy and two had tonsillectomy and adenoidectomy. We consider recurring otitis media and deafness, which were present in 18 patients, as strong indications for adenoidectomies, at least to help provide an adequate airway. If nasal surgery is done before the allergic symptoms are controlled, there is likely to be recurrence of lymphoid tissue and an increase in allergic symptoms. If surgery is done when the allergy is quiescent, much improvement may be expected. It was interesting to compare the small number of children, 14 out of 182, who had had surgery before their first visit in 1957 with a similar but slightly older group of 153 allergic children, reviewed 15 years ago, of whom more than one-half had had tonsillectomy before the possibility of allergy was ever considered.

In this group of 182 preschool children, only 19 or about 10 per cent had either no allergy or at most a suspected allergy. This is in marked contrast to our experience with a group of infants referred for allergy study, of whom more than one-third had nonallergic problems.[1] This points up the increased ease with which an accurate diagnosis of allergy can be made in the preschool child as time clarifies the course of an illness and as the child's increasing age makes examination more reliable and the incidence of allergy greater.

Indications and Symptoms of Allergy

The recognition of allergic rhinitis begins first with suspicion on the part of the physician that he is not dealing with an infection. The doctor may find that his records on the child include formula and feeding problems, bowel disturbances, spitting, colic and a transient tendency to seborrhea or facial rash. The patient may be recalled as a snoring, nose-rubbing "mouth breather" with recurring otitis media, for whom adenoidectomy was considered and for whom antihistamines and antibiotics were frequently prescribed.

Head bumping, "rocking" at night, constant sniffling and nose twitching are some of the irritating mannerisms which may even suggest a nervous tic. The mother may have commented on the child's susceptibility to "colds" when exposed to a sudden temperature change, and "colds" may have interfered with a regular immunization routine.

In an occasional patient as the fifth or sixth

TABLE 3

SIGNS AND SYMPTOMS OF ALLERGIC RHINITIS

Recurring or constant "colds"
Nasal itching and rubbing; sneezing
Mouth breathing
Adenoidal facies
Pale, edematous turbinals
Mucoid, stringy, neutral mucus
Eosinophilia of nasal smear and blood

year approaches, there may appear some vague, protracted, ill-defined symptoms suggestive of rheumatic fever. Aching legs, fatigability, sweating, low grade fever, tachycardia, dark circles under the eyes, poor appetite, occasional abdominal pain, a tendency to chronic sore throat, mild nasal discharge, and lymphadenopathy, especially around the cervical region, may be present. The clinical picture remains unchanged for months, and the gamut of objective tests done to establish the presence of rheumatic fever gives negative results. The allergic basis for this illness eventually may be suspected if an eosinophilia is found, if a particularly severe cold is accompanied by wheezing, or if a rash follows the use of an antibiotic.

This could be a composite picture of the history of an allergic child in whom an allergic rhinitis develops. Although no one of the symptoms or observations alone spells allergy, the combination of several of these traits should make one highly suspicious of allergy (table 3).

Confirmation of these suspicions rests on the physical examination and some characteristic laboratory tests. In allergic rhinitis with nasal obstruction of any degree or duration, a typical allergic or adenoidal facies develops, with flattened malar bones, a narrow, pinched nose, and a high dental arch with some degree of malocclusion. The nasal mucous membrane is typically pale, approaching the color of the skin in a white child and of the buccal mucous membrane in a colored child. The swollen turbinals may have a bluish-gray translucent appearance or they may be a dull red if there is complicating infectious, vasomotor or chemical rhinitis.

The allergic secretion is a characteristically stringy, tenacious mucus, alkaline in reaction and nonirritating to the nares. In quiescent allergic rhinitis we have noted cobwebby strands of mucus bridging the airway between the septum and turbinal. When stained with any stain appropriate for staining blood cells, this mucus is shown to contain eosinophils. Examination of the nasal smears, as described by Hansel,[2] is one of the easiest and simplest of office procedures and is amazingly consistent as an indication of nasal allergy. When the typical physical appearance and the laboratory findings are coupled with the suggestive history, the diagnosis of allergic rhinitis, even in the very young child, should not be difficult.

Determination of Asthma

Asthma is a more serious menace to health and normal activity than is allergic rhinitis. Therefore, the physician must be alert to recognize early asthmatic tendencies in children in order to prevent permanent changes and damage to the lungs.[3]

The diagnostic features of asthma in the older preschool child are those of the obstructive emphysema of asthma at any age (table 4). The pattern of recurring attacks of dyspnea, with expiratory wheezing and typical prolonged expiratory musical rales relieved completely or in large part by bronchodilators differs distinctly from other pulmonary conditions seen at this age.

In the younger preschool child from two to four years of age, it may be extremely difficult to diagnose asthma. The typical wheezing attack, rapid in onset, may be replaced by several days or nights of hacking or of croupy intractable coughing, with only a little demon-

TABLE 4

SIGNS AND SYMPTOMS OF ASTHMA

Obstructive emphysema and wheezing
Expiratory and inspiratory rales
Abrupt or gradual onset
Response to bronchodilators
Characteristic sputum
Eosinophilia of blood and sputum

strable emphysema. There may be inspiratory as well as expiratory musical rales, with a degree of prostration beyond that expected for asthma. Fever, an uncommon finding in uncomplicated asthma in older patients, is one of the common early symptoms in young children. This, coupled with the rapid, shallow respirations, may suggest bronchiolitis or pneumonia, and one frequently notes that these children have a history of repeated episodes of pneumonia.

Atelectasis is another common complication of acute asthma which occurs frequently at this age. In this series of patients, 13 of the 107 children whose complaints were primarily pulmonary had proved atelectasis. In several others the severity of the symptoms and the clinical course suggested that episodes of collapse of a portion of the lung had occurred at some time during their illness. In six asthmatic children there was roentgenographic documentation of one or more episodes of atelectasis in the past. In five other children with asthma, including one who also had a congenital cardiac condition, roentgenographic procedures showed atelectasis at the initial examination. In two children, who were referred for allergy study but who were found to have fibrocystic disease of the pancreas, atelectasis was present at the first visit.

It is important to realize that atelectasis complicating an attack of asthma may make symptoms refractory to conventional treatment. The converse is also true; that is, atelectasis due to any cause, such as a foreign body or a mechanical obstruction, may result in wheezing which can easily be mistaken for asthma in the young child. In spite of current reluctance to overexpose children to x-rays, we feel that the child suspected of having asthma, or with persistent wheezing, coughing, or lower respiratory symptoms of any sort, should have both posteroanterior and lateral x-rays of the chest.

Every effort should be made to obtain sputum for cultures and for gross and microscopic examination. In asthma, the same type of gelatinous, clear, colorless material obtained from the nose is present as twisted, stringy casts of the bronchioles. It is often coughed up as little pellets, and if teased out in a small amount of water, the characteristic corkscrew, bulging and constricted spindle of Curschmann's spirals will be seen. Microscopic identification of the Charcot-Leyden crystals and eosinophils can quickly, painlessly and inexpensively lead one to a correct diagnosis of asthma. The secretions in asthma differ from those in any other pulmonary condition, and these characteristics are present to some degree even in the presence of complicating infection.

Even in young children every effort should be made to detect the specific etiologic factors in allergic rhinitis and asthma. This can usually be done by skin tests, using the scratch, intradermal or passive transfer technic. An adequate interpretation of the meaning of these tests, the places in which the suspected allergen may be found, and the best means of either avoiding the allergens or desensitizing the patient to them should be clearly explained to parents. If precautions against exposure are not completely effective, the youthfulness of the patient does not contraindicate undertaking desensitization.

It is equally important to evaluate the role which nonspecific factors such as temperature change, humidity, intercurrent infection, fatigue and emotional stress play in the actual precipitation of symptoms and to spell this out to the parents. An understanding of this dual (allergic and nonspecific) causation of symptoms makes for more effective management of the allergic child. If parents can be made to realize that an underlying allergic sensitization has established an asthmatic reaction pattern, and that because of this change a respiratory infection will result in asthma plus the infection, and that chilling will be followed by rhinitis or asthma, then they can better understand why these nonspecific factors affect their child differently than a normal child.

Treatment

It is impossible to outline any specific program of medication which will suit all patients with the same clinical condition, although we know that certain preparations are best suited for certain symptoms. Thus we think of anti-

histamines for allergic rhinitis and urticaria and to decrease itching in eczema. Nearly 200 different preparations containing antihistamines are listed in the current "Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals," which does not include the many "over-the-counter" antihistamines. There are four main chemical types of antihistamines,[4] represented by BENADRYL®, PYRIBENZAMINE®, CHLOR-TRIMETON® and a miscellaneous group which includes THEPHORIN® and PERAZIL®. If one antihistamine does not completely control the symptoms or produces unwanted side effects, then a drug from a different chemical group should be prescribed. Various compounds which include ephedrine, pseudoephedrine and NEO-SYNEPHRINE® hydrochloride are often helpful in controlling nasal allergy. Topical medications such as nasal drops, sprays and jellies have a place in short-term treatment, but do not lend themselves to prolonged use since they may provoke a chemical rhinitis or further water-soak an edematous membrane. It is my personal opinion that steroids, administered orally or by injection, have no place in the treatment of nasal allergy.

The child with asthma needs both immediate and long-term treatment. The various bronchodilators, such as epinephrine, ephedrine, isopropylarterenol, NORISODRINE® sulfate, norepinephrine and the xanthines, are helpful in most children and should be used in a dosage and by a route suitable for the patient's age, weight and severity of symptoms. The expectorants and mucolytic agents have an important place in treating the bronchitic or chronically asthmatic child. The asthmatic patient often should have his medication changed periodically to avoid developing a tolerance or refractoriness to some useful drug.

We feel that the use of steroids orally or by injection in allergy is presently in urgent need of critical reappraisal. In this series we saw many children whose growth ceased with the initiation of steroid therapy and who developed a Cushing syndrome, hypoproteinemia, increased susceptibility to infection, and a myriad of unwanted complications while on steroids. We do not deny that steroids are or frequently appear to be lifesaving, and we do not hesitate to use them in desperate situations; however, we also see many more children whose health is endangered by their prolonged and overenthusiastic use. We feel that they have no place as a substitute for rigorous efforts to control specific exposures and as a replacement for specific treatment. Medical experience with steroids is still too limited to know the effects in the later life of children who have used these powerful agents for considerable periods of time.

There is much concern at present over the hazards of radiation on the growing child; real as this danger may be, much of this fear is based on speculation. Awareness of the danger of long-term ill effects from steroids, on the other hand, is based on the certain knowledge of immediate ill effects, on fatalities, and on side effects which threaten health and growth after a few months of use. We must begin to heed the warnings given by even the manufacturers of steroids and use these agents only for major and not minor allergic crises. The allergic child who has specific treatment for his specific sensitivities is still the child who has the most certain opportunity to overcome his allergy.

Summary

A review of the records of 182 preschool children from two to six years of age who were referred to an allergy clinic during 1957 showed a ratio of four boys to three girls. The group of 57 five to six year old children was slightly larger than the three other age groups, which consisted of between 40 and 43 patients.

Allergy could be established as a cause for symptoms in 90 per cent of these children. In contrast, one-third of a group of infants under two years of age, who were recently studied for suspected allergy, had no allergic disease.

Allergic rhinitis was the most common problem, being present in 111 patients; as expected, multiple allergic conditions were noted in even the youngest patients. Asthma was present in 107 children and was complicated by atelectasis in 13; eczema was present in 34 children, and other allergic conditions occurred infrequently.

The diagnosis of allergic rhinitis and allergy depends on a complete history, physical and laboratory findings, and simple diagnostic tests which apply to allergic rhinitis and asthma, since these are the major allergy problems in the preschool child.

The management of allergy of the respiratory tract should include specific treatment to remove the offending allergens or to desensitize the patient in preference to relying exclusively on symptomatic measures.

From this survey, the conviction is gained that the many side effects and complications of steroid therapy are such that steroids should be used only for major allergic crises and not as a substitute for specific therapy.

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Postgraduate Clinical NOTES

122. PSYCHOSOMATIC MEDICINE

The clinician who successfully practises psychosomatic medicine must be a good all-round doctor. We take it for granted that he will know how the body functions. He should certainly take a pride in being "good at physical signs," but he must not let them shut him off from the rest of reality. He must be interested in how the mind works, and he may find it natural to believe, as modern philosophers do, that the working of body and mind cannot be separated.

One of the great difficulties in being a good all-round doctor is lack of time—time in which to find out as much as possible about the patient. Unfortunately, when time presses the doctor tends to take up his pen. How much easier and quicker it is to give the child with "growing pains" an aspirin preparation—looking like melted ice cream and tasting of raspberries—than to find out why he is emotionally insecure. Not 1 child of every 20 children with growing pains has organic disease; but some are kept by us from school, some are put to bed, and many are dosed.

John Apley, Psychosomatic disorders in children, *Lancet*, March 28, 1959, pp. 641-644

Carcinoma of the Breast

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A great deal of controversy surrounds the question of the effectiveness of treatment of breast carcinoma, particularly radical surgical procedures in early cases.

The results of simple mastectomy followed by radiotherapy are compared with those of radical surgery in two series of cases, in Edinburgh and at the Mayo Clinic, respectively; despite the many variables involved in such a comparison, the figures are of interest because of their similarity.

Endocrine therapy in metastasizing breast cancer has profoundly altered malignant growth in some cases. Hypophysectomy is gaining favor and appears to be superseding adrenalectomy.

HAROLD W. RODGERS

OUR thinking in carcinoma of the breast, which seemed so static a few years ago, has undergone two important changes during the last decade or so. First, the use of radiotherapy has again been brought very much into prominence by the work of McWhirter in Edinburgh and by the development in general of radiotherapeutic technics. The other change has been the attack on metastasizing carcinoma of the breast by endocrine therapy, in the form of administration of certain endocrine products or of removing those glands responsible for producing breast-stimulating hormones. This second field, which, like radiotherapy, is not new, has been given great impetus by Huggins' work in Chicago. But so far no one has claimed that altering the endocrine status can cure carcinoma of the breast; for cure we still depend on surgery or radiotherapy or some combination of the two.

Before going on to discuss the present position of surgery and radiotherapy, we might

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mention two things. The first is that chemotherapy has so far not produced good results in breast carcinoma. The results of chemotherapy have, of course, been spectacular though not permanent in the more disseminated forms of malignant disease such as leukemia and lymphoma. The second topic that deserves mention is the natural history of the disease.

Natural History of the Untreated Disease

This is a difficult subject. There is no report, nor is it likely that there will be one, of large unselected series of cases of cancer of the breast which have deliberately been left untreated. However, Greenwood, Daland, Wade and others have reported on the natural history. Their accumulated figures show that the average survival in untreated cancer is 38.5 months from the appearance of the first symptoms to the death of the patient. However, so variable is the disease that one patient survived more than 35 years after diagnosis and several survived more than 15 years. McKinnon, trying to evaluate the effectiveness of the cancer control programs in Ontario, Canada, said, "Unfortunately, in the province of Ontario the records of cancer mortality did not show any decline in any age group." McKinnon does not consider it likely that an absolute increase in breast cancer reported would have been apparent had it not been for the control program which focused attention on the subject. He concluded his report by arguing with Park and Lees: (1) It has not been proved that the survival rate of cancer of the breast, using the five year survival as an index, is affected by treatment at all; (2) the evidence strongly suggests that treatment is quite ineffectual in reducing the incidence of death from metastatic spread; (3) if treatment is in any way effective, the effectiveness cannot be greater than that required to increase the over-all five year survival rate by more than 5 to 10 per cent.

McKinnon claims that many of the stage I cures are in fact cures of a type of cancer that is neither of short duration nor a lethal form of the disease: "Thus, while the Stage I cancers of any series may possibly be or include non-metastasising types, the level trends in mortality in spite of an increase in the proportion of cancer treated as Stage I, the lack of any other credible explanation for the wide difference in proportions classified as Stage I in different clinics, and the excess of Stage I in some series over what could be reasonably expected in metastasising cancers point consistently to the Stage I cancers in some series including, almost unquestionably, non-metastasising, non-lethal lesions. Thus, because of their dubious character, survivals of Stage I 'cancers' cannot be considered conclusive evidence of the value of treatment in an early stage of lethal cancer."

While McKinnon and others who have expressed similar views have undoubtedly made a valuable contribution in pointing out that some patients with five year "cures" would have survived without treatment, they seem to have disregarded four things.

1. They have overlooked the fact that the incidence of carcinoma at various sites changes. For instance, it is accepted beyond question that the incidence of lung carcinoma has increased, but carcinoma of the mouth has decreased. Similarly, the Registrar General's figures show that in England and Wales there has been an increase in deaths from cancer of the breast, the standardized rate per million rising from 292 in 1930 to 356 in 1953. Surgeons and radiotherapists would certainly claim that the death rate would have increased even more had it not been for their treatment.

2. They have assumed that a stage I growth of a nonmetastasizing type will stay relatively benign and localized if untreated. It is known that tumors in many other sites may alter in character with the passage of time, and although "benign" initially eventually become metastasizing tumors.

3. If a growth already has spread to the axillary glands at the time of treatment, it seems reasonable to assume that untreated it would continue to spread beyond the axilla and cause death. The five year survival rate in cases with axillary metastases from the breast has been reported by many surgeons (Haagensen 40 per cent, Harnett 44 per cent).

4. McKinnon points out quite correctly that

TABLE 1

CARCINOMA OF THE BREAST; STAGE, GRADE AND PROGNOSIS (ALL TREATMENTS)*

STAGE	GRADE	CASES	FIVE YEAR SURVIVALS (PER CENT)	CASES	TEN YEAR SURVIVALS (PER CENT)
I	1	125	84	87	56
	2	144	69	78	49
	3	78	64	47	45
II	1	81	74	48	50
	2	162	46	99	27
	3	118	25	73	10
III	1	53	70	39	46
	2	95	26	59	14
	3	74	16	53	11
IV	1	7	43	2	50
	2	37	5	26	4
	3	28	4	22	5
TOTAL		1,002	50	633	32

*From H. J. G. Bloom, Middlesex Hospital.

in many early cases, especially with short histories but without discoverable metastases, the patients die after what appears to be adequate treatment, presumably because of blood-borne metastases that occurred while the case was yet clinically early. He quotes Bloom as saying that "we are compelled to adopt the view that the outcome in mammary cancer is determined largely by the histological type of growth rather than by prompt treatment as soon as the lesion is discerned." The outlook is determined not only by histologic grading but also by the clinical stage the disease has reached. This is shown by Bloom's own figures from the Middlesex Hospital (table 1); 64 per cent of patients with stage I, grade 3 tumors survive five years, while 70 per cent of those with stage III, grade 1 tumors survive for the same time. It seems likely that a combination of clinical staging with histologic grading must offer the best available indication of prognosis at present.

Staging

Many methods of determining the degree of advancement of carcinoma of the breast on clinical grounds have been tried and numerous systems put forward. Indeed, one was put forward at the international cancer conference during the summer of 1958. So far no international agreement has been reached. In general, however, it may be said that stage I represents an early growth without evidence of spread anywhere; stage II, involvement of axillary glands; stage III, local fixation of the breast to surrounding tissues, and stage IV, distant metastases, by blood dissemination, lymphatic spread or even direct extension.

Surgery and Radiotherapy

In Great Britain the usual practice is to treat all stage I and stage II cases, and sometimes stage III cases, with surgery and irradiation. Some surgeons do not ask for radiation treatment in stage I cases, and this practice is more prevalent in North America than in Great Britain. The main question at issue is whether or not radiotherapy adds much to the prognosis in these cases. This is a subject which McWhirter in Edinburgh has tackled with great vigor.

The Edinburgh practice is to do a simple mastectomy and follow this with radiotherapy in all cases except those with proved distant

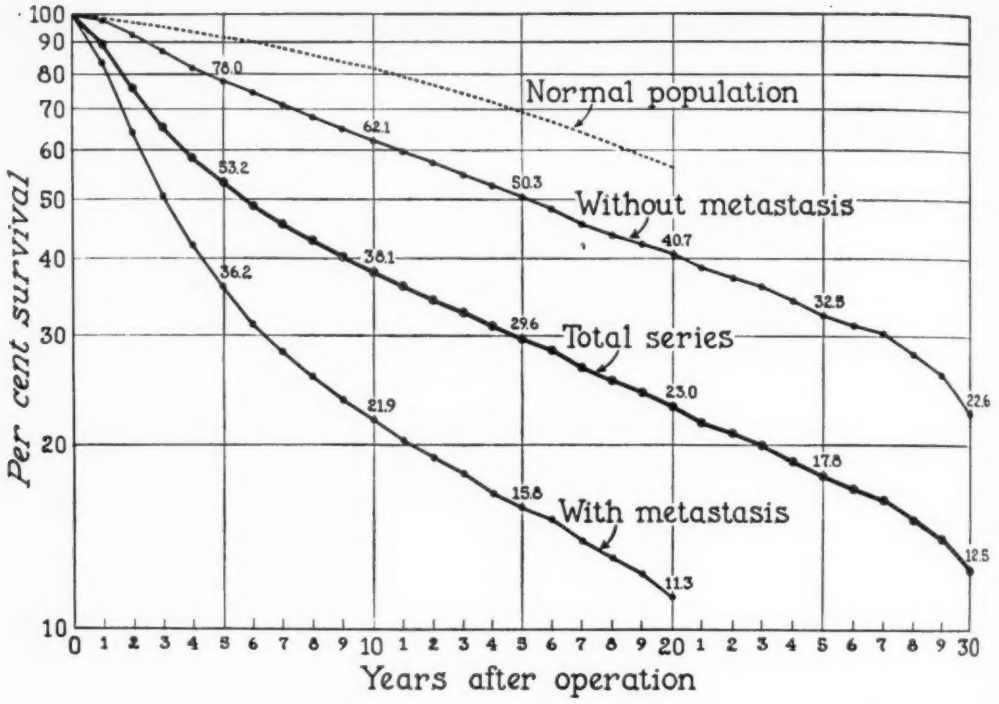

FIGURE 1. Survival of patients with carcinoma of the breast according to presence of metastasis (Mayo Clinic series).

metastases and a few cases of very obese women in which it is difficult to be accurate in radiologic technic. In any discussion on radiotherapy it must be fully appreciated that the treatment must be carried out with anatomic and physical exactitude. The placing of the beam must be precise and the output of the tube and efficacy of filtration must be measured. In the past, much radiotherapy has been given without this quite necessary degree of accuracy. At the Mayo Clinic, radiotherapy is used only palliatively and reliance is placed on a well-executed radical removal of breast and axillary contents.

The Mayo Clinic results are given in figure 1, and the Edinburgh results in tables 2 and

TABLE 2

RESULTS OF TREATMENT OF CARCINOMA OF THE BREAST IN EDINBURGH SERIES; ALL CASES OF PRIMARY BREAST CANCER RECORDED

STAGE OF DISEASE	1941-1947 FIVE YEAR CRUDE SURVIVAL RATE			1941-1942 TEN YEAR CRUDE SURVIVAL RATE		
	Total	*Number Alive*	*Per Cent Alive*	*Total*	*Number Alive*	*Per Cent Alive*
Operable	1,063	612	58	254	99	39
Locally advanced	546	162	30	157	23	15
Distant metastases present	273	12	4	69	0	
TOTAL	1,882	786	42	480	122	25

TABLE 3

CLINICAL AND PATHOLOGIC GROUPING OF A LARGE SERIES OF CASES OF BREAST CANCER (MCWHIRTER); ALL CASES OF PRIMARY BREAST CANCER RECORDED IN THE PERIOD 1941 TO 1947

OPERABLE, 56 per cent	
Axillary glands histologically negative, 40 per cent of operable cases, 25 per cent of total cases	Simple mastectomy as effective
Axillary glands histologically positive, 60 per cent of operable cases, 34 per cent of total cases	
Glandular involvement confined to axilla, 14 per cent	*Disputed group*
Positive supraclavicular or internal mammary glands, 20 per cent	Radical mastectomy fails
LOCALLY ADVANCED, 29 per cent; DISTANT METASTASES, 15 per cent	Radical mastectomy does not apply

3. Table 3 helps explain the important "operable" group mentioned in table 2. What seems to stand out from these two very careful surveys is the similarity of the results achieved at these two excellent centers. The results of two independent series examined clinically cannot be strictly comparable. Further, the classification of the one is purely clinical, and of the other histologic as well as clinical. What is worthy of note in the Edinburgh series is that in the very unfavorable locally advanced cases the five year survival rate is 30 per cent.

It seems, then, that surgical removal is applicable to the early case, particularly in the lateral half of the breast whence it is most likely to spread to the axilla. In the medial half of the breast, mediastinal spread is so likely that radiotherapy should be used whether the operation is radical or not, for operation is unlikely to succeed.

Radical surgery is most unlikely to succeed where axillary glands are clinically recognizable as malignant, and in those cases after removal of the breast with the contained primary tumor, and without disturbing the axilla, the whole area should be irradiated.

Before attempting to compare the figures from such centers as Edinburgh (radiotherapy) and the Mayo Clinic and Presbyterian Medical Center in New York (surgery almost exclusively for early cases), it is important to realize that these different series are not easily comparable. There may be some essential difference in incidence of cancer between one place and another, and one cannot expect the clinical criteria of selection to be identical. What is of interest is not so much the dissimilarity of the figures as their similarity; but certain differences are of interest.

Berkson and associates have compared a very large series of cases at the Mayo Clinic with a large Edinburgh series. All but a very small percentage of the patients in the Mayo Clinic series had radical mastectomy and therefore must have been predominantly in the operable group. On the other hand, 29 per cent of the cases in the Edinburgh series were locally advanced and 15 per cent of the patients had distant metastases, a total of 44 per cent, almost all of which cases would have been unsuitable for radical surgery. If we accept Haagensen's criteria for unsuitability for radical operation, there might be others in the Edinburgh series which should be excluded as unsuitable for comparison. It is difficult, therefore, to see how such very diverse groups can be usefully set beside each other.

We do not propose to go into details of the methods of surgery and the various radiotherapeutic technics which can be employed. It seems reasonable that much of the present argument about methods of treating breast cancer should be resolved if two things were done: (1) if a series of cases in a center handling a large number of patients each year were treated by simple mastectomy and radiation and a parallel series were treated by radical surgery only. This can be done only when the medical and ancillary staff concerned are convinced of the need for this information and are honestly disquieted by our present ignorance; (2) if we had a better understanding of the natural pathology of the disease.

Since Handley first demonstrated the involvement of metastases of the supraclavicular and parasternal lymph nodes in nearly 50 per cent of cases in which the axilla was apparently normal on ordinary examination, many

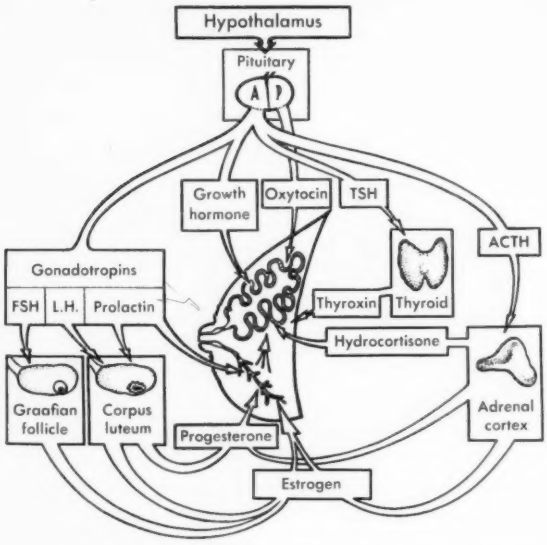

FIGURE 2. Relationships of the breast to the endocrine glands.

people have felt concern about the usefulness of the radical operation as a routine. The super-radical surgery practiced by Urban, Wangensteen and others is logical in view of the now known routes of dissemination of the tumor, but it is mutilating surgery inappropriate to the routine of an ordinary hospital practice. Moreover, the assessment of long-term results is not yet possible and the initial operative mortality is high, up to about 13 per cent.

McWhirter too has pointed out that the usefulness of the radical operation is limited whereas the procedure of simple removal of the breast, which in the vast majority of cases gets rid of the primary tumor, followed by radiation is the most reasonable and widely applicable treatment. It may well be that dissection of the axilla in advanced cases disseminates tumor cells. That this is a very real risk has been shown in postoperative studies of the peripheral blood in patients with cancer in various sites. Local mastectomy, with less trauma of the skin, also allows the high dosage of radiation to be given with less risk of radiation damage to the skin. McWhirter states that if the destruction of tumor in the axilla is to be attained a minimum dosage of 3,750 r must be given in three weeks or equivalent dosage in a longer period. If such dosage levels are attempted after radical surgery, complications such as frozen shoulder, brachial neuritis and edema of the arm are likely. So much is this true that it is doubtful if radiotherapy is worthwhile after radical surgery. If the surgeon has no faith in his operation it is difficult to see a reason for using it.

Berkson has suggested that removal of the bulk of the malignant process is valuable even though some tumor cells are left behind. To the best of our knowledge it is virtually certain that such tumor cells will continue to grow and will kill the patient if they disseminate whether their number is large or small.

It is not possible to apply any method of treatment in a wholesale way, and individual variations must be made. For example, many obese patients are not suitable for the Edinburgh treatment when x-rays are used at ordinary voltage; or if the tumor were radioresistant, surgery would be required. Nevertheless a rational policy which can be varied is needed.

Chest wall recurrences after surgery can be dealt with by local radiation or further surgery, depending on the nature of the original treatment. Palliative relief can be given by x-ray therapy to bony metastases if these are localized to treatable areas.

Endocrine Treatment of Metastasizing Breast Cancer

Treatment of advanced breast cancer by altering the endocrine environment has met increasing success since it was first attempted 60 years ago, and more recently has attracted a great deal of attention. It has been clearly shown that removal of certain endocrine secretions on the one hand and giving of certain endocrine products, mostly steroids, on the other have been able to cause in some cases a profound alteration of malignant growths, usually a regression. The growths which have shown this best have been carcinomas of the breast and prostate.

The fundamental explanation for these facts is unknown, but we can get a great deal of information from study of the physiology of the breast and its endocrine relationships.

Figure 2 illustrates diagrammatically the more important of the known relationships of the breast to the endocrine glands. The direct influence of the higher centers of the brain on the breast is unknown, but possibly the hypothalamus controls breast development and function by modifying hypophysial secretions. Some of the hormones of the pituitary act on the breast directly and some act indirectly, as shown in figure 2, by controlling the action of the ovaries and the adrenals. These glands secrete both estrogen, which causes duct proliferation, and progesterone, which promotes acinar development. Ovarian action is subservient to the pituitary gonadotropins, which are follicle-stimulating hormone, luteinizing hormone and prolactin. Stimulation of the graafian follicle by FSH produces estrogen, while L.H. and prolactin govern the corpus luteum and thereby control both progesterone and estrogen. Adrenal secretion is dependent on ACTH again derived from the pituitary. An important point to bear in mind is that estrogen secretion by the adrenals goes on long after the menopause. Prolactin also has an important direct effect on the breast, playing a major part in growth and lactation, along with estrogen and progesterone. Growth hormone has an important but nonspecific effect on the breast without which normal development cannot occur. Thyroxin is capable of raising a subnormal milk secretion to normal levels; it cannot, so far as is known, however, raise the yield above normal.

Evidence implicating estrogen in the development of mammary cancer has accumulated in studies of both man and lower mammals. Removal of the ovaries at birth in mice in which the susceptibility to breast cancer is high protects them against subsequent development of the disease, while injections of estrin into male mice can produce breast cancer. In human beings oophorectomy for any cause decreases the likelihood of subsequent development of primary cancer of the breast. There is evidence, as yet inconclusive, which suggests that the growth hormone may also be implicated.

Broadly speaking, endocrine treatment of metastasizing breast cancer can be divided into two classes: (1) administration of hormones and (2) surgical removal or destruction of the endocrine glands believed to help sustain breast cancer. Let us consider first the administration of hormones.

Testosterone—The method of action of this hormone is uncertain, but it appears to be either by a peripheral antagonism to estrogen or by suppression of the pituitary. Even if regression of the cancer itself fails to occur, the patient frequently notices a feeling of general well-being. Ninety-five per cent of the remissions so induced lasted less than one year, but sometimes on withdrawal of the hormone a further improvement ensues.

Testosterone may produce various side effects, including masculinization, which causes coarse skin, acne, temporal alopecia, hirsuties, deepening of the voice, clitoral enlargement, and considerable increase in libido; rise in serum calcium in patients with bony metastases, which can cause nausea, vomiting, diarrhea, weakness, apathy, renal damage and even peripheral circulatory failure; and fluid retention, of which some degree always occurs but which may be dangerous in patients with cardiovascular disease.

There are three main methods of administration, but the first two are used much more commonly than the third: (1) Intramuscular injections of 100 mg. testosterone propionate may be given twice or three times a week. It is advisable to attain a dosage of 3500 to 4000 mg. over a period of about four months, and after that gradually to reduce the dose. If the patient is not showing response in six weeks, some other method of control should be considered if the general condition permits. (2) Methyltestosterone may be administered orally in a dosage of 50 to 100 mg. a day. The tablets are dissolved sublingually. This treatment, while it permits self-administration, is more expensive. (3) Pellets of 500 to 750 mg. are implanted subcutaneously. This method has the disadvantage that if unpleasant side effects result it is not possible to interrupt the effect of the drug.

Durabolin—Recently a new preparation, Durabolin, has been marketed by Organon. Ltd. It may be given intramuscularly in 25

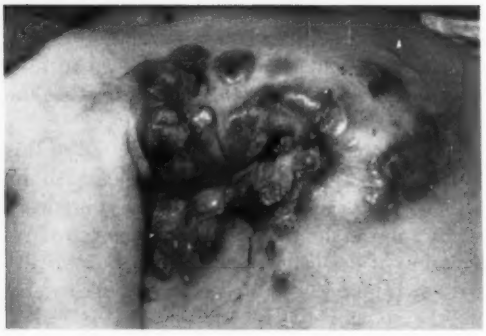

FIGURE 3. Photograph taken March 28 showing extensive cutaneous secondary lesions in the chest wall and axillary region. Patient was an 80 year old woman who had had carcinoma of the breast for three years. Therapy with stilbestrol was given, 20 mg. three times a day. The improvement is shown in figure 4.

FIGURE 4. Photograph taken June 11, 75 days later.

mg. doses once or twice a week. It is said to be free from the masculinizing effects of testosterone, and this is obviously very desirable. However, experience with it is short and its value cannot be properly assessed.

Unfortunately, only a very small proportion of patients who have metastatic breast cancer respond to androgen therapy, but Raven has reported very long-term survivals, in a few cases up to five years and more.

Estrogens—That estrogens themselves may be of use is paradoxical. The mode of action of this hormone, itself implicated in the carcinogenic process, is far from clear. It may be that in large doses it possesses a direct antimitotic effect on dividing cells. Alternatively it may act by depressing secretion of certain other hormones by the pituitary. Seventy per cent of remissions induced by estrogen are followed by relapse after one year, although, as with testosterone, further relief may be obtained on withdrawing the hormone. It is more useful in those women who are well past the menopause in the seventh and eighth decades of life (figures 3 and 4).

Side effects include nausea, vomiting, general malaise, excessive pigmentation of the areola, and uterine hemorrhage. These effects may also be observed on discontinuing the therapy. Fluid retention also may occur.

Estrogens are nearly always administered orally. The most common and cheapest method is to give diethylstilbestrol, 10 to 20 mg. daily. Nausea is common with these substances and can be avoided to some extent by dispensing them in keratin-coated capsules.

Other preparations used are Dinoestrol, 10 mg. daily, and ethinyl estradiol, 3 mg. daily. These rarely if ever produce irritation of the gastric mucous membrane. They are, however, expensive.

Estrogens also can be given parenterally in the form of estradiol benzoate, 5 mg. twice or three times weekly intramuscularly, or estradiol dipropionate, 5 mg. at the same interval.

Cortisone—Cortisone presumably acts by pituitary suppression. It has, however, been shown to increase gonadotropin secretion while also depressing thyroid function, neither effect being theoretically desired.

Prednisone and thyroid hormone—Prednisone, the analogue of cortisone which causes less fluid retention, combined with thyroid hormone appears to be very successful in Lemon's hands. Possibly, however, many of the so-called remissions are subjective only and due rather more to the feeling of well-being engendered by the corticosteroid than to any effect of the treatment itself. Prednisone acts by depressing secretion of ACTH by the pituitary and thus of adrenal estrogens. However, it does cause an increase in secretion of gonadotropins and so, if the ovaries are capable of responding to this, estrogen secretion will be maintained. In patients less than 60 years of age the ovaries should thus be re-

moved. As prednisone also interferes with thyroid function, thyroid hormone should also be administered. The suggested dosage is prednisone 30 mg. three times a day and thyroid 1 gr. three times a day. This is a very large amount of prednisone, complications are very likely to occur, and the patient will require strict supervision.

Surgical removal or destruction of endocrine glands—Surgical treatment was initiated in 1896 by Beatson. He carried out oophorectomy, an operation which probably owes its effect to the removal of a source of estrogen. The adrenals are an additional source of estrogen, and probably this is the reason only one-fourth of the patients benefit by this operation.

When adrenalectomy (frequently combined with oophorectomy) became possible, much better results were obtained (Huggins). Calculated from most of the major published series the average rate of remission is about 50 per cent.

Preoperative treatment is simple and consists of ensuring an adequate hemoglobin level and administering cortisone for the three days prior to operation; doses vary, but most commonly 100 mg. is given daily, the last injection shortly before the operation. It is essential to have an intravenous infusion going, through which norepinephrine may be administered should the blood pressure fall during or after operation. This complication is rare but may be catastrophic if it occurs, and because of it a careful watch must be kept on the blood pressure and pulse for at least 72 hours postoperatively. One hundred milligrams of cortisone is given by injection every six hours for the next 24 hours, and then if the patient is well enough it may be given orally. The dosage is steadily reduced over the next five days to the maintenance level of 25 mg. twice daily. Desoxycorticosterone acetate or salt tablets are rarely required.

It is most important to warn both the patient and her doctor that there must never be any interruption of the cortisone maintenance therapy and that any infection or other stress must be properly met with an increase in the dosage. Failure to comply with this requirement leads to a serious collapse if not death.

TABLE 4

RESULTS OF ADRENALECTOMY

SERIES	NUMBER OF CASES	NUMBER OF REMISSIONS
Pyrah, 1954	75	39
Cade, 1957	170	102
Huggins and Dao, 1953	25	10
Pearson, 1955	38	17
Huggins and Bergenstal, 1952	61	25
Galante, 1957	79	30
Taylor, 1956	60	26
Hellstrom, 1957	166	84

Table 4 gives the results of most of the major series of adrenalectomies.

Following the combined operation, which was expected to remove all estrogens from the body, it was found that the hormone frequently persisted in the urine. It is thought that its origin is in the adrenal cell rests which are shown to be present in the retroperitoneal tissues. These cell rests presumably undergo hyperplasia due to increased ACTH secretion by the pituitary following adrenalectomy.

The next logical step was removal of the pituitary, first carried out by Luft and Olivecrona in Stockholm. This operation, which is gaining favor in many centers, now appears to be superseding adrenalectomy. The operation has two advantages, in that it removes ACTH which acts both on normal and on ectopic adrenal tissue, and it removes prolactin and growth hormone.

As with all forms of endocrine therapy used today, there is as yet no satisfactory method to select those patients likely to benefit from the procedure. It does appear, however, that patients in whom the metastatic disease is confined to bone do rather better than those in whom spread is present in lungs, liver and, particularly, brain. That is not to say that none of this group will have remissions, but the probability is rather less. In addition, the further the patient is past the menopause the less probable becomes the possibility of any benefit.

Several means exist for the performance of this operation. First there is the surgical ap-

TABLE 5

RESULTS OF HYPOPHYSECTOMY

SURGEON	YEAR	TECHNIC	NUMBER OF CASES	NUMBER OF REMISSIONS
Atkins	1957	Surgery alone	30	20
Radley-Smith	1957	Surgery alone	60	34
Kennedy et al.	1956	Surgery alone	28	18
Forrest	1957	Yttrium^{90} implant	42	9
		Radon implant	36	10
Luft and Olivecrona	1957	Surgery alone	197	110
Pearson et al.	1956	Surgery alone	41	21
Ray	1956	Surgery alone	67	36
Edelstyn et al.	1958	Surgery and yttrium^{90}	36	26

proach pioneered by Luft and Olivecrona (1953) and second the transnasal insertion of yttrium^{90} pellets into the pituitary gland through a special introducer (Forrest, 1957). In practice it has been shown that after either type of hypophysectomy the estrogen secretion may still persist. The source of estrogen is naturally of very great importance and there are several possibilities. The ovaries and adrenals may be capable of functioning in the absence of pituitary stimulus. Pituitary tissue may be present ectopically outside the sella and may be capable of taking over function of the normal gland. A third possibility is incomplete removal of the pituitary gland itself.

With regard to the first possibility, animal experiments and observations in human beings suggest that the ovaries and adrenals are not capable of functioning independently. Extrasellar pituitary tissue does exist, but it is still uncertain whether it is capable of normal function. Lastly, incomplete removal of the pituitary has frequently been discovered post mortem.

The best means of complete pituitary destruction is a combination of surgery and radiotherapy, which is giving promising results. Following as complete a surgical removal as possible, yttrium^{90} suspended in wax is packed into the pituitary fossa and then is brought closely into contact with any remaining pituitary tissue. The intense, though short-lived, radiation is sufficient to destroy the residual tissue. This procedure, as judged by postmortem investigation and postoperative endocrine assays, seems to yield a very high proportion of complete destructions (Edelstyn and associates, 1958).

Preoperative and postoperative therapy is as a rule simple, and no problems should arise if there is adherence to certain points. Fifty milligrams of cortisone is given on the day preceding operation and again immediately before operation. Twenty-five milligrams of cortisone is given every four hours for the first 24 hours postoperatively, then every six hours for 24 hours, and then every eight hours. By the end of one week the patient should be on a maintenance dose of 25 mg. twice daily. As with adrenalectomy, it is of paramount importance never to cease the cortisone medication, and to increase it during any infection or stress. This cautionary measure cannot be sufficiently emphasized.

Thyroid medication is necessary, and generally speaking 1 gr. three times daily is sufficient, the level of the blood cholesterol being a satisfactory guide to dosage.

PITRESSIN® tannate in oil may be required in the immediate postoperative period for the polyuria and polydipsia of diabetes insipidus which often develops. It may, however, not be needed for several days. If it is given within 36 hours of operation, great care should be taken to avoid causing excess fluid retention, as this may aggravate the edema of the brain that usually occurs after this operation.

Table 5 gives the results of most of the major series of cases in which hypophysectomy has been done.

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Postgraduate Clinical NOTES

123. TUMORS OF COLON AND RECTUM

Evidence indicates that adenomas (adenomatous polyps) of the colon and rectum are true tumors and not a reaction which follows a diffuse inflammatory process. The incidence of adenomas of the colon and rectum increases with age. There is histologic and cytologic evidence that adenomas of the colon and rectum may undergo malignant transition. Collateral data in regard to age of the patient and sites of predilection support the concept of the intimate relationship of adenomas to carcinoma of the large intestine. Both adenomas and adenomas with carcinoma may be of diverse shapes and sizes. Some adenomas, especially in the rectum, are papillary and spread peripherally. However, all adenomas of the colon and rectum appear to have a common mode of origin. Carcinoma of the large intestine may arise directly from the mucosa, but many carcinomas arise in adenomas. Carcinoma *in situ* in adenomas of the colon and rectum is not capable of metastasis, but carcinoma with invasion of the core or stalk is capable of metastasis. Examination of superficial bits of tissue may be misleading, but if the pathologist has examined (and knows he has examined) the entire adenoma, he can estimate accurately the potentiality in respect to metastases.

Elson B. Hellwig, Adenomas and the pathogenesis of cancer of the colon and rectum, *Diseases of the Colon and Rectum*, January-February 1959, pp. 5-17

Treatment of the Shoulder–hand Syndrome

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Prophylactic treatment of the shoulder-hand syndrome following acute myocardial infarction or anginal attack should start while the patient is confined to bed.

Active motion of the arm helps overcome splinting, atrophy and osteoporosis, and may overcome lymphatic and venous stasis. Concomitant use of cortisone lessens pain and spasm.

A PAINFUL upper extremity is a relatively common sequel of myocardial infarction and other types of arteriosclerotic heart disease. The severity of the affliction varies from localized pain and the impairment of shoulder motion to the complete clinical picture of the shoulder-hand syndrome, including edema of the hand followed by osteoporosis, atrophy, and flexion deformity of the fingers.

The cause of the shoulder-hand syndrome remains uncertain. Johnson,[1] Askey,[2] Hilker[3] and deTakats[4] postulated that dysfunction of the autonomic nervous system is responsible for the changes that occur in the tissues. Edeiken[5] believed that afferent impulses from the sympathetic nerve fibers are caught in the cardiac scar and that this is responsible for the reflex changes that occur in the upper extremity. However, Steinbrocker, Spitzer and Friedman[6] expressed doubt that sympathetic nerve dysfunction is an adequate explanation for these changes. Russek and associates[7] believed that increased spasm of the muscles of the shoulder girdle as well as immobilization may be responsible for these changes.

I believe that the shoulder-hand syndrome is partially due to immobilization of the arm in the first few days after an attack of myocardial infarction or angina pectoris and to the continued limitation of use of the arms. Immobilization initially leads to shoulder pain. If effective therapy is not instituted promptly, the use of the hand is decreased, and a mild, barely pitting edema develops over the hand. Pain then occurs in the elbow, wrist and fingers. Further immobilization occurs, and is followed by atrophy of muscle and bone. Finally, Dupuytren's contracture may occur.

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This opinion has been somewhat reinforced by the observation of patients who are afraid to elevate their arms during an acute episode of myocardial infarction. They fear that such motion may further injure their heart. Relatives and some nurses share this belief and are astonished when the patients are told not only to elevate their arms frequently but to use them rather vigorously. Patients frequently lie in bed two to four weeks without extending their arms, and they thus splint the glenohumeral articulation. It is also possible that disturbance of the return of venous blood and lymph may play some part in the production of pain and atrophy.

Treatment of the shoulder-hand syndrome has varied between the use of procedures directed at the sympathetic nervous system, for example, blocking the stellate ganglion, and the use of corticosteroids. Steinbrocker, Neustadt and Lapin,[8] and Evans[9] have obtained satisfactory results with the former type of treatment, and Russek and associates[7] and Rosen and Graham[10] have obtained favorable results with the latter type. Edeiken[5] was not impressed with steroid therapy, but believed that the use of heat, analgesics and exercise will produce satisfactory results.

This paper is based on the results of treatment in 19 cases in which the patients had the shoulder-hand syndrome of varying severity. Sixteen of the patients were men and three were women. The ages of the patients ranged from 52 to 74 years, and the average age was 63 years. In 14 of the 19 cases, the pain in the shoulder developed between one month and two years after an episode of myocardial infarction. In the remaining five cases, the signs and symptoms were compatible with arteriosclerotic heart disease, and episodes of angina had occurred in some of these cases. The syndrome involved the left arm in 12 cases and the right arm in seven cases.

The pain was described as burning, dull and deep. Although the pain originally occurred in the shoulder, it frequently involved portions of the hand. Many of the patients noted that the pain was worse when they were in bed, particularly when they were lying on the affected side. In 14 cases, the pain in the shoulder was associated with variable edema of the hand, which often was transitory. In four cases, severe pain in the shoulder was associated with marked edema of the dorsum of the hand. At times, tender areas were noted, particularly over the triceps muscle and the ulnar side of the hand. In one case, the syndrome was in the early phase of stage 3, and was associated with deformity of the left hand and some osteoporosis.

The patients were treated for periods ranging from four months to two years. The average duration of treatment was 16 months. Treatment included the use of active motion and administration of steroids. The syndrome recurred in five cases. The time at which it recurred was quite variable. In two of the five cases, the recurrent lesion involved the arm that had been affected originally; in the remaining three cases, it involved the opposite arm. Both arms were not involved simultaneously in any of the cases.

Treatment

Prophylactic treatment is very important. In cases of acute myocardial infarction, movement of the arms should be started as early as possible, that is, when shock and the effect of narcotics have waned. Patients are told to raise both arms over their head several times a day and to lie on their back frequently with their hands clasped behind their head. This is a valuable means of preventing splinting of the shoulder and it does not entail much effort for the recumbent patient. It is surprising that so much attention is devoted to movement of the lower extremities during prolonged rest in bed and that so little concern is given to movement of the arms. As mentioned previously, getting the patient to move his arms frequently involves overcoming some of his fears as well as those of nurses, friends and relatives. If pain in the shoulder does not develop while the patient is in the hospital or after his dismissal, no further prophylactic measures are instituted except to emphasize to the patient the value of free motion of the arms and the possibility that pain in the arms may develop if he inhibits motion of the arms.

After pain develops in the shoulder, active

motion still is the most important part of the treatment. If the patient is seen soon after the development of the pain, it is relatively easy to get him to move his arms. However, in cases in which syndrome is more advanced, movement of the arms often is painful, and the patient's cooperation must be sought. It is important to instruct the patient in the correct motion of the arm. As the arm is abducted and elevated, many patients attempt to attain full elevation of the arm by rotating the scapula. This undoubtedly sends the arm higher, but it causes a cessation of extension at the glenohumeral joint. To increase elevation of the arm, the patient frequently tilts the body laterally away from the affected side. Such maneuvers accomplish little.

To teach the patient how to extend his arm correctly, he should be instructed to stand with his chest against the wall and to elevate his arm by advancing his fingers up the wall. Here again, it is important to prevent dorsiflexion of the back, for this also compensates for limitation of motion at the shoulder joint. Patients are instructed to perform these exercises for 15 minutes at least three times a day. In addition, they are encouraged to swing their arms freely rather than to hold the painful arm in a fixed position. The patients also are encouraged to use the affected arm for performing routine tasks.

The second therapeutic measure consists of the administration of corticosteroids. When treatment is begun, 50 mg. of cortisone is administered intramuscularly once a week. It is not necessarily injected into the painful arm or into tender areas. It was necessary to administer hydrocortisone intramuscularly in only one case, and it was administered only once in this case. During the time that cortisone is being used, 5 mg. of prednisone (METICORTEN®) is administered three times a day by the oral route. As improvement occurs, the intervals between the injections of cortisone are increased and the dose of prednisone is decreased. Finally, all medication is stopped either because of recovery or lack of improvement.

Certain physiotherapeutic measures, particularly local application of heat, massage and passive motion, are not used. I believe that these measures not only are unnecessary but actually contribute to prolongation of the disability by discouraging the use of active motion and by encouraging the patient to rely on passive motion.

The results have been most satisfactory. In more than half of the cases in which a complete remission was obtained, relief became evident within two weeks after treatment was started and it usually was complete within six weeks. Several of the patients expressed gratification for the ability to sleep again.

Twenty-four courses of treatment were employed in the 19 cases. Five of the 24 courses were necessitated by a recurrence of the syndrome. Eighteen of the courses produced a complete remission which lasted for at least six months. Five of the courses produced a partial remission; that is, some pain still was present but the relief was substantial. In one case, the treatment did not produce any significant improvement. In this case, the syndrome was in an advanced stage and was associated with osteoporosis, edema of the hand, and an early flexion contracture of the fourth and fifth fingers of the left hand.

Case Reports

I shall report three cases which will illustrate the results obtained with the treatment I have described.

Case 1—A 61 year old man, who had been a coal miner, was admitted to the hospital in January 1957 because of severe substernal pain which had been present for one hour. The pain was relieved by the administration of morphine. Physical examination revealed faint heart sounds but no murmurs. The patient was moderately dyspneic, and rales were present at the base of each lung. An electrocardiogram revealed myocardial infarction. Roentgenographic examination of the chest disclosed extensive pneumoconiosis of both lungs. The patient recovered uneventfully and was dismissed from the hospital five weeks after his admission.

In March 1957, moderate anginal pain occurred, and the patient remained in bed for two weeks. In July 1957, pain occurred in the

right shoulder. Although the pain originally was mild, it became moderately severe. The patient soon found that he could not extend his right arm without discomfort, and the pain had extended to the arm and hand. On September 4, 1957, examination revealed slight tenderness of the right shoulder and tender areas over the triceps muscle and the wrist. Moderate edema was present in the right hand. Abduction of the arm was limited to an angle of 45 degrees. The patient walked with the involved arm hanging by his side or else supported it with his left hand. Cortisone and prednisone were administered as described previously, and the patient was instructed to perform the exercises which also have been described.

Marked improvement occurred within a week, and the patient was able to elevate the arm to an angle of 90 degrees. The administration of cortisone and prednisone was continued. The patient subsequently found that he could once again comb his hair with his right hand. The interval between the injections of cortisone was increased to two weeks, and subsequently to three weeks, and a single dose of 5 mg. of prednisone was given once a day.

All treatment was discontinued on November 13, 1957. Since that time, the patient has been able to get along very well. He is able to sleep without pain and can elevate his arm to an angle of 180 degrees.

Case 2—A 60 year old plumber had had an infarction on the anterior wall of the myocardium in October 1957. He had been treated at his home with rest in bed. He had remained at home for four weeks, and subsequently had resumed activity gradually.

The patient was seen in my office in March 1958 because of pain in the left shoulder which was aggravated by rest. Electrocardiography revealed nonspecific changes compatible with arteriosclerotic heart disease. Examination disclosed tenderness of the left shoulder and slight edema of the left hand. Abduction of the arm was limited to an angle of 90 degrees.

Cortisone and prednisone were administered in the manner described. By May 1958, the pain had disappeared completely, and it has not recurred.

Case 3—A 77 year old man had a severe attack of substernal pain on October 12, 1957. After he was admitted to the hospital, electrocardiography revealed extensive infarction on the anterior wall of the myocardium. Congestive heart-failure developed while the patient was in the hospital, but it was relieved by the administration of digitalis. Subsequently, 500 mg. of DIURIL® (chlorothiazide) was administered once a day by the oral route.

In January 1958, pain and limitation of motion developed in the right shoulder. Cortisone and prednisone were administered, and active motion was started. The patient improved almost immediately. The interval between the injections of cortisone was increased, and all therapy was stopped in May 1958. The patient has had no symptoms since that time.

Summary and Conclusions

The cause of the shoulder-hand syndrome remains uncertain. It is possible to treat this syndrome effectively without blocking the stellate ganglion. Prophylactic treatment consists of early activity of the arms after an attack of acute myocardial infarction. This treatment is of paramount importance, and it should be begun while the patient is still confined to bed.

As soon as pain occurs in the shoulder, active motion of the arm should be instituted to overcome splinting, atrophy and osteoporosis, and perhaps to overcome lymphatic and venous stasis. The concomitant use of cortisone lessens pain and spasm. Although this appears to be the only action of cortisone in cases of the shoulder-hand syndrome, I believe that it is helpful since it permits active motion with lessened pain. When cortisone was administered in the manner described, it did not cause generalized edema or other signs of heart-failure, and there was no evidence that it had any effect on the heart-failure that was present. It did not cause any of the other side effects attributed to the steroids.

Twenty-four courses of treatment were employed in 19 cases. Eighteen of the courses produced a complete remission which lasted for at least six months. Five of the courses produced a partial remission. In one case, the treatment did not produce any significant im-

provement. This treatment is effective, especially if it is started early in the course of the syndrome.

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Postgraduate Clinical NOTES

124. SURGERY IN PARKINSON'S DISEASE

My colleagues and I are of the opinion that tremor and rigidity can be altered, diminished or abolished by [this] type of surgical treatment. We have, in fact, observed ballistic movements in patients in the postoperative period. They were particularly severe in one case, but in all they have been transient and have not become serious, permanent problems. Many characteristics of the Parkinson syndrome are unaffected by our surgical efforts. While these operations have been accomplished in most cases without difficulty, they may be hazardous because of danger to life and to motor function and because, if done on the dominant side, they may markedly affect personality, mentality and speech function. We therefore recommend this type of surgical treatment cautiously. We feel that patients who are mentally or physically deteriorated cannot be benefited appreciably by surgical means. We therefore prefer to select candidates for surgical treatment who are not completely disabled. We also prefer that one side be less affected than the other, and that tremor and rigidity be dominant factors. We favor doing the operation on the nondominant hemisphere and not bilaterally. Most of our patients who have undergone surgical treatment have had Parkinson's syndrome; though we have operated on patients with other disorders of movement, we have not had sufficient experience to comment regarding such cases. We have had no clinical experience utilizing ultrasonic energy or radioactive material to produce these lesions. We consider these efforts to be still in the investigative stage.

Collin S. McCarty, Surgical treatment of hyperkinetic disorders, *Proceedings of the Staff Meetings of the Mayo Clinic*, July 8, 1959, pp. 343-349

Chronic hidradenitis suppurativa causes painful discomfort as well as social embarrassment. An intensive search for adequate therapy has not yielded a widely accepted method for treating the different stages of this disease. A surgical modification which drained the chronic foci of infection and eliminated the cavity lining was successful in 35 patients treated by the authors. They recommend that even a single chronic lesion should be treated by this method.

Treatment of Chronic Hidradenitis Suppurativa; Surgical Modification

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THE pathologic entity of hidradenitis suppurativa has been known for more than 100 years.[1,2] It is most often characterized by extreme chronicity and resistance to a wide variety of therapeutic modalities. The search for adequate therapy has been intensive and has been made by investigators in the fields of dermatology, surgery and radiology.

The purpose of this paper is to summarize the previous therapy employed, with particular emphasis on the surgical methods, and to present the results in 35 cases in which we utilized a surgical modification that we do not believe has been precisely duplicated in the past.

It seems necessary to mention briefly the pathologic physiology of this disease before undertaking a discussion of various therapeutic measures. The primary site of involvement is the apocrine sweat glands, which are located in the axillary, anogenital and mammary regions, as well as some other regions. Although the basic cause is not known, we feel that there is a blockage of the ducts of these glands, which is followed by inflammation and secondary bacterial invasion. In the acute stage, the condition is characterized by nonsuppurative, tender, nodular lesions, which we prefer to call apocrinitis. In cases of chronic hidradenitis suppurativa, there is a tendency for mul-

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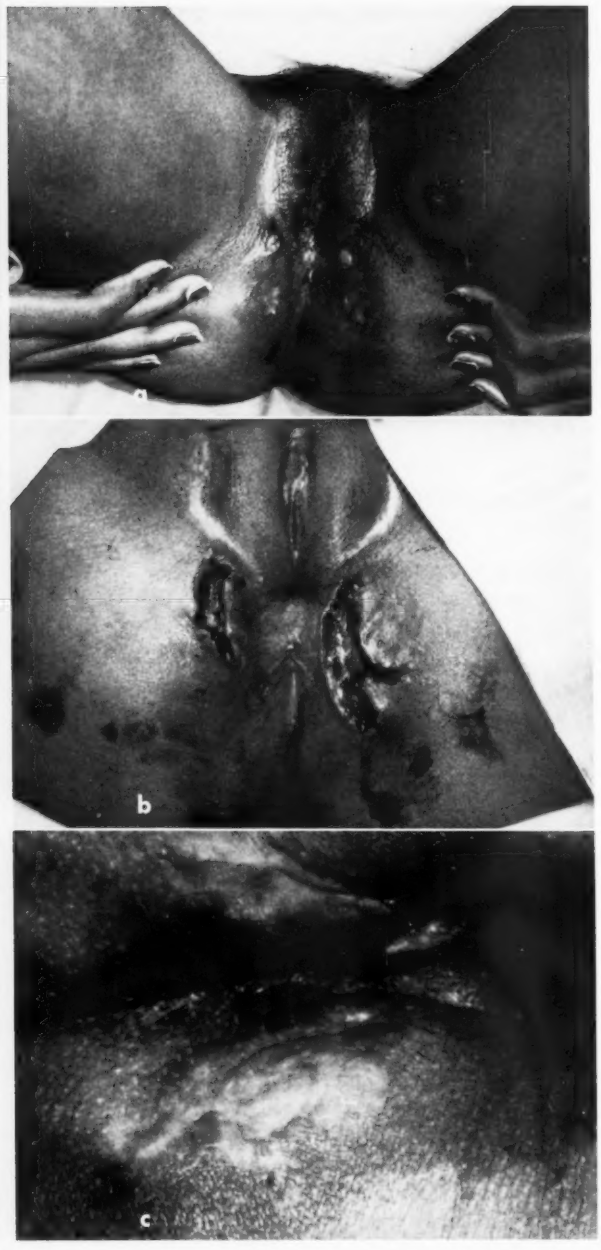

FIGURE 1. Relatively mild hidradenitis suppurativa of the perianal region of a 17 year old Negro girl; a. appearance before treatment; b. appearance at the time of exteriorization and electrocoagulation; c. appearance approximately six weeks after the operation.

tiple sinuses to develop irregular and often hypertrophic scars occur frequently, and the lesions have a tendency to become very resistant to any type of conservative treatment. In cases of advanced hidradenitis suppurativa, the lesions may dissect laterally to form pockets filled with pus and a rather characteristic gelatinous material. It should be noted that the advanced lesions dissect only to the lower portions of the dermis and rarely, if ever, into the subcutaneous tissue.

In cases in which chronic lesions become extensive and are treated inefficiently, anemia and cachexia may develop. In these cases, marked toxic, systemic reactions may develop from secondary infection. If drainage from extensive lesions is not adequate, the patient ordinarily does not improve until this is achieved by surgical means. In a review of the literature in the English language to 1933, when the first article was published by Lane,[1-6] the impression is gained that nonsurgical methods, with the exception of roentgen therapy, have been singularly ineffective in cases of chronic and extensive disease.

The multiplicity of nonsurgical therapeutic approaches will not be listed here. Although Brunsting[3] has stated that the use of roentgen rays has shown promise in the treatment of this problem and has at times resulted in an apparently satisfactory result, he cautions that surgical intervention often becomes necessary. In summary, the various surgical approaches employed in the past have consisted of the following: incision and drainage,[6,7] unroofing the lesions and allowing them to heal by secondary intention;[3,8] surgical incision, followed by curettement and packing;[1] electrosurgical incision, followed by curettement without packing;[4] and wide surgical excision and skin grafting.[2,3,5-7,9]

Material and Method of Study

The 35 cases used in our study varied from those in which there was a single lesion or sinus to those in which there were dozens of openings which might extend to involve regions as large as the entire buttocks. In these cases, the duration of the disease ranged from a few months to 25 years.

FIGURE 2. Advanced hidradenitis suppurativa of the right axilla of a 31 year old Negro man; a. appearance before treatment; b. appearance at the time of surgical exteriorization and electrocoagulation (patient is in supine position and the right arm is in extreme abduction); c. appearance approximately eight weeks after the operation.

In all of the cases, we used a surgical modification that consisted of the following steps:

1. A probe was inserted into each individual sinus tract, and the superficial tissue was incised so as to effect complete exteriorization. Any redundant tissue also was removed during this stage of the procedure.

2. The multiple cavities containing pus and gelatinous material were adequately drained, and the lining was curetted thoroughly.

3. The entire exteriorized area was extensively coagulated with a bipolar current. This has a threefold purpose, which will be discussed later.

4. After the operation, antibiotics, such as a combination of neomycin, polymyxin and bacitracin, were applied locally, and, beginning on the first day after the operation, hot compresses or sitz baths were used three times each day.

Although this procedure can be performed with local anesthesia, general anesthesia certainly is more desirable if the lesions are multiple or extensive.

Results

Figure 1 shows the appearance of a rather mild type of hidradenitis suppurativa before operation, at the time of operation, and after operation. Figure 2 shows a more advanced form of the disease involving the axillary region.

In some cases, the patients were completely relieved by the operation; in other cases, a few new lesions developed. These lesions were treated in the same way as the original lesions. Complete healing occurred within three weeks to three months after the operation. The average time required for complete healing was about four to six weeks. In all of our cases, the patients were greatly improved even if they were not completely relieved of the disease. It is worth mentioning that the patients were extremely grateful. One patient with extensive involvement of the vulva had been unable to assume the sitting position for 10 months before the operation, but she was completely rehabilitated.

Comment

There appears to be no unanimity of opinion regarding the most ideal method of treatment of the different stages of hidradenitis suppurativa. In our experience, the acute stage (apocrinitis) usually does not require surgical treatment. However, epilation of the hair over the nodules is often beneficial in promoting resumption of glandular secretion and resolution of the disease process. This is probably due to the fact that this epilation relieves the blockage of some of the apocrine ducts, which in many instances empty into the hair follicles.

In most of our cases of chronic and advanced hidradenitis suppurativa, the patients have had much painful discomfort as well as social embarrassment owing to continuous and malodorous drainage, which has been present for many years. Commonly, such patients have sought medical attention numerous times previously and have experienced repeated therapeutic failures when conservative and ineffective surgical methods have been tried. We feel that our results in such cases have been quite gratifying. Since one of us (J. F. M.) has used this technic for eight years, it has withstood the test of time.

Even if only a single chronic lesion exists, it should be treated as soon as possible by the method outlined, because of the probability of peripheral extension to form multiple sinus tracts. This same procedure should be followed if there is a recurrence at the periphery of a previously treated site.

The steps in our treatment, as we have outlined them, serve to accomplish drainage of the chronic foci of infection and elimination of the cavity lining which seems to promote the re-formation of lesions. The bipolar electrocoagulation serves to stop bleeding, helps destroy the lining of the cavity, and minimizes postoperative pain by alteration of the nerve endings.

It is our opinion that this procedure is superior to any of the other modalities which we have utilized or observed. While wide surgical excision and skin grafting may be necessary ultimately in cases of very extensive disease, it is preferable to reserve this as a last resort, owing to the greater magnitude of the procedure and the fact that when glabrous skin is grafted into certain intertriginous sites, such as the axilla, the feel of the area is often unnatural and uncomfortable.

Conclusion

We believe that the surgical modification we have described is a worthwhile contribution to the search for an effective treatment of chronic hidradenitis suppurativa.

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Common Misconceptions Concerning the Skin

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The common opinion concerning the benign nature of diseases of the skin is erroneous. Many serious systemic diseases have cutaneous manifestations. Numerous misconceptions exist regarding diagnosis and treatment of acne, plant and contact dermatitides, warts, psoriasis, etc. Steroids should be used with caution in managing diseases of the skin.

ARTHUR B. KERN

THROUGHOUT the ages, man's scientific advance has involved a discarding of superstitions, folklore and concepts proved to be incorrect. Unfortunately, a number of the false ideas have persisted and have been passed along from one generation to another. Dermatologic knowledge is similarly enmeshed in a network of misconceptions, fallacies and fables. This is particularly true of the lay person's understanding of the skin and its disorders. However, it is also true to a lesser degree of the nondermatologic physician. It is my intention to review some of these common misconceptions.

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Cutaneous Manifestations of Internal Disease

I would first like to point out that the skin is not just an envelope or wrapping to hold the internal organs together. Neither is it simply a decorative façade to aid in the attraction of one sex for the other. Instead, it is one of the largest body organs. Its weight is three times that of the liver. It is an organ performing important functions of secretion, temperature regulation, protection, control of water output, storage, metabolism and immunologic

TABLE 1

INTERNAL DISEASES ASSOCIATED WITH CUTANEOUS MANIFESTATIONS

1. Systemic infections
   a. Subacute bacterial endocarditis
   b. Rheumatic fever
   c. Polyarteritis nodosa
   d. Tuberculosis
   e. Erythema nodosum
   f. Sarcoidosis
   g. Lupus erythematosus
   h. Dermatomyositis
   i. Scleroderma
2. Disorders of endocrine glands
   a. Thyroid dysfunction
   b. Addison's disease
3. Metabolic disorders
   a. Diabetes mellitus
   b. Lipoidosis
   c. Gout
   d. Avitaminosis
   e. Amyloidosis
   f. Porphyria
4. Purpura
   a. Infectious or toxic conditions
   b. Thrombocytopenic purpura
   c. Allergic conditions
   d. Hemophilia
   e. Rendu-Osler-Weber disease
5. Internal neoplasms
   a. Cutaneous metastasis of carcinoma
   b. Lymphoma
   c. Reticuloendotheliosis
   d. Acanthosis nigricans
6. Disorders of the nervous system
   a. von Recklinghausen's disease
   b. Adenoma sebaceum
   c. Hemangioma
   d. Trophic ulcer
7. Psychiatric disorders
   a. Alopecia areata
   b. Neurotic excoriation
   c. Neurodermatitis
   d. Delusion of parasitosis
   e. Dermatitis factitia
8. Disorders of the gastrointestinal tract
   a. Sprue
   b. Intestinal polyposis
   c. Ulcerative colitis
9. Disorders of the liver and pancreas

activity. With this understanding of the skin as a vital functioning organ, it is obvious that there must be a close relation between the skin and the viscera. In other words, the common conception that diseases of the skin are unrelated to the other body processes is erroneous. Not only is there an intimate connection between these two, but the skin is often the first organ to show signs of systemic disease. Accordingly, dermatologic training in recent years has stressed this bond between dermatology and internal medicine. It is also imperative that the nondermatologist recognize the importance of the skin in relation to those diseases with which he is primarily concerned.

Space does not permit a consideration of the many cutaneous manifestations of internal disease. However, I would like to include a table (table 1) which, although by no means complete, does include some of the systemic diseases which have significant cutaneous manifestations.

After study of this table, it is obvious that the common opinion concerning the benign nature of diseases of the skin is in error. I would like further to call attention to several other diseases, not included in the table, which primarily involve the skin and which may cause death. These are pemphigus, mycosis fungoides, squamous cell carcinoma, melanoma, deep fungous infections and exfoliative dermatitis.

Round Lesions

One of the most common misconceptions concerning the skin is that every round lesion is the result of ringworm or fungous infection. Whereas it is true that many superficial fungous infections do have a round configuration, most round lesions are not due to fungous infection. Among these might be mentioned psoriasis, granuloma annulare, nummular eczema and erythema multiforme. The importance of proper differential diagnosis is apparent with the realization that application of the strong fungicidal drugs will aggravate most of the nonmycotic eruptions.

Acne

Acne is an extremely common disorder, yet the misconceptions in regard to it are quite numerous. Stated simply, acne is the result of two alterations in the skin: first, an increased activity of the sebaceous glands, and

second a hyperkeratotic narrowing of the pilosebaceous orifices. It is not the result of failure to wash the face often enough. It is not the result of improper diet. It is not the result of sexual frustration, and along the same line marriage is not the best treatment for acne. It will not cease at the time of onset of the menses.

How should the youngster with acne be handled? It is most important that the child should not simply be told that acne is the result of his age and that he will grow out of it. Treatment of all but the mild types of acne is imperative for two reasons: First, because the youngster with acne is generally extremely self-conscious concerning his appearance and to prevent psychic trauma, treatment is important. The second reason is that treatment will minimize the damage and prevent or lessen the degree of scarring. At this point, I would like to mention the misconception that roentgen therapy causes scarring. This idea has arisen because such treatment is usually reserved for the more severe types of acne. These are the types that cause large and deep destructive lesions. Such lesions necessarily heal with scarring. After roentgen therapy, the active lesions disappear and only the scars remain. Before therapy the patient was primarily concerned with the active lesions, but after treatment he notes only the scars and blames his treatment for them. However, it is the acne lesion itself and not the therapy that is responsible for scarring.

Plant Dermatitis

Another common disorder of the skin and one about which there are many fallacious beliefs is so-called poison ivy dermatitis. Let me first point out that there are many plants which can cause reactions of the skin. The most common offender in New England is poison ivy. Very often the patient will ask whether the eruption is due to poison ivy, poison oak or poison sumac. However, the cutaneous reaction is the same regardless of which plant is responsible, and the specific nature of the offending plant cannot be determined by the type of eruption produced. Blister formation is usually a part of this plant dermatitis. Many persons believe that the fluid within the blister contains the offending agent and that it will, if allowed to contact normal areas, produce new lesions. This, of course, is not so. The blister contains only serum which is produced as part of the allergic reaction. Accordingly, the dermatitis cannot be spread by the lesions or the fluid within them, and the dermatitis is not contagious insofar as other persons are concerned.

The use of strong soap as treatment must be mentioned. Thorough washing of the skin with soap and water immediately after possible exposure to sensitizing plants has long been recommended in order to remove the plant resin from the skin. This approach to prophylaxis has, however, been distorted to the point where many persons will use laundry and other harsh soaps on the skin which has already erupted. Such treatment only results in aggravation of the dermatitis. Another form of therapy which should be discarded is the injection of plant extracts. Experience has shown that such extracts not only have no beneficial effect but, in fact, will frequently cause a severe exacerbation of the eruption as well as fever, leukocytosis and other systemic effects. These extracts should be employed only for the prevention of plant dermatitis, never for treatment.

Warts

A considerable assortment of myths and fables has arisen about another common dermatologic disorder, the wart. To begin with, let me point out that many lesions of the skin which are casually referred to as warts are in reality nevi, papillomas, hemangiomas, etc. There are actually four main types of verrucae: (1) the common wart or verruca vulgaris, (2) the juvenile or flat wart, (3) the plantar wart and (4) the so-called venereal wart. Warts are all of viral origin, and it is likely that either the same virus or closely related ones are the responsible agents.

In regard to the treatment of warts, in general, it may be stated that some form of therapy is indicated. The specific modality depends on the type of wart, number of warts, location of the lesions, and the age of the pa-

tient. It is a fact that spontaneous involution does occasionally occur. However, in a given case, one never knows in advance whether this will be the course or whether the lesions will enlarge and multiply. Accordingly, early treatment rather than a period of waiting is usually advisable.

Psoriasis

Many misconceptions exist concerning psoriasis, a disease of unknown origin. The most significant fallacy is in regard to the effectiveness of treatment. Although psoriasis sometimes is resistant to treatment and difficult to manage, it frequently will improve to a certain degree and it may even clear up completely with the proper therapy. Time after time, I have seen psoriatic patients who had suffered from itching and embarrassment for many years and had postponed seeking aid because they had been told that nothing could be done to help them. Within a short time after treatment was started, many of these patients were free of itching, and further treatment caused partial or complete clearing of the lesions in many cases. It is true that psoriasis may recur after the lesions have disappeared. A physician does not withhold treatment from a patient with congestive heart-failure because the heart-failure may recur. Similarly, one should not withhold treatment from a patient with psoriasis.

Contact Dermatitis

I frequently have heard the statement that a given substance could not be responsible for contact dermatitis, because the patient had been handling it for many years before the dermatitis developed. This statement is based on the erroneous idea that contact dermatitis can be induced only by an agent to which the patient has been exposed recently. On the contrary, however, a person may have contact with a given substance for many years before sensitivity develops. It may perhaps clarify the matter if it is stated that a minimum of seven days is required before sensitization can occur, but that there is no maximal period within which it must develop. In other words, a person can manifest a sensitivity reaction to a particular agent on re-exposure after seven days or after 5, 10, 20, 25 or more years.

Genital Lesions

On numerous occasions I have seen patients with genital lesions who consulted me on their own accord or were referred to me, in both instances with the diagnosis of venereal disease in mind. Whereas it is correct to consider every genital lesion as venereal until proved otherwise, I wish to point out that numerous nonvenereal diseases may produce genital lesions. Common among these are drug eruptions, psoriasis, lichen planus, pityriasis rosea, scabies and herpes progenitalis.

Positive Wassermann Reactions

A very important misconception concerns the persistence of a positive Wassermann reaction in cases of syphilis in which the patients have been treated adequately. I frequently have seen patients who had been treated two, three or even four times because a serologic test for syphilis had remained positive. Experience has shown that a quantitative rather than a qualitative serologic test is necessary for the proper evaluation of the results of treatment. If a quantitative test is performed, it can be demonstrated that the titer or degree of positivity in a case of primary or early secondary syphilis will fairly rapidly fall to zero. In late secondary syphilis, many months may be required. In latent syphilis, the fall in titer following therapy is extremely slow, and the reaction may never become negative. Most important is that after treatment the patient should be followed by periodic tests, and that, as long as the quantitative titer remains the same or is falling, no further therapy is indicated or is of any benefit. Treatment is necessary only when the titer shows a definite and continuing rise, indicating a relapse.

Dermatoses of the Feet

Whereas the most common dermatosis involving the feet is probably athlete's foot, I wish to call attention to the fact that numerous other disorders may involve the skin of these areas. With this in mind, error in diagnosis and resultant mistreatment may be avoided.

One of the disorders of the feet most commonly misdiagnosed as dermatophytosis is dyshidrotic eczema. This is an entity which is characterized by development of redness, blisters and itching, most commonly observed on the soles and on the sides and plantar surfaces of the toes. It is frequently accompanied by similar lesions on the palms, sides of the fingers, and palmar surfaces of the fingers.

Contact dermatitis, secondary syphilis, psoriasis, lichen planus and pustular bacterid are some of the disorders which may also occur on the feet and be confused with dermatophytosis. Treatment of these conditions with fungicidal drugs would have a strong aggravating effect. What has been said in regard to the feet applies equally as well to the hands. Actually, fungous infections of the hands are uncommon, and most eruptions of these parts are the result of dyshidrotic eczema or contact dermatitis.

Otitis Externa

A frequently observed condition in dermatologic practice is otitis externa. In a large percentage of cases, the patient has previously been treated with fungicides. However, never in my experience has such an eruption been due to fungi. Careful laboratory studies have confirmed the absence of pathogenic fungi in such cases. When there is evidence of infection as manifested by pain, redness, swelling and discharge, bacterial infection by *Pseudomonas aeruginosa* can usually be demonstrated. However, in most cases of otitis externa, the disease is in the chronic stage and is associated with itching, redness, scaling and perhaps slight oozing. In such cases, there is no infection. Instead, the eruption is a seborrheic dermatitis, psoriasis, atopic eczema or contact dermatitis. It is obvious, therefore, that fungicidal drugs should not be used in the treatment of otitis externa.

Contagion

There is a prevalent belief among the laity as well as among nondermatologists that skin diseases are highly contagious. Such a misconception may be due to the fact that most people associate skin disorders with dirt, filth and venereal disease. However, only a very small percentage of the common dermatologic diseases are contagious. These would include scabies, pediculosis, impetigo, warts and fungous infections. The bulk of the dermatologist's practice, made up of contact dermatitis, seborrheic dermatitis, acne, atopic eczema, neurodermatitis, psoriasis, urticaria and drug eruptions, represents disorders which are in no way transferable. The concept, therefore, of the highly contagious nature of skin diseases should rightfully pass into oblivion.

Steroidal Therapy

In conclusion, I would like to make a plea for considerable caution regarding the use of steroids in the management of diseases of the skin. Unfortunately, ACTH and cortisone and its derivatives are not the panacea that many physicians have been led to believe. Steroids in the form of an ointment or a lotion are beneficial in the management of certain disorders such as contact dermatitis, neurodermatitis and atopic eczema. However, they are valueless in a host of dermatoses. Despite this, I have seen many patients with psoriasis, lichen planus, ichthyosis, granuloma pyogenicum and numerous other entities who had been treated by the local application of steroids. In those instances in which such medication is indicated, it should be kept in mind that it is only one factor in therapy. In cases of contact dermatitis, for example, a search for and removal of the offending agent are important. In neurodermatitis, relief of emotional tension is vital. In atopic eczema, food, contact and emotional factors must be considered.

In regard to the systemic use of steroids, I would like to state that it also has a limited place in the management of diseases of the skin. With the exception of acute urticaria and serum-sickness-type reactions, pemphigus, disseminated lupus erythematosus, exfoliative dermatitis, severe drug eruptions, generalized lichen planus and severe herpes zoster, one should hesitate before prescribing these potent drugs. Systemic administration of steroids should not, in my opinion, generally be employed for infantile eczema, contact dermatitis, psoriasis or atopic eczema. I

mention these four conditions in particular because steroids have been used frequently for their management. As regards infantile eczema, I feel that steroids are definitely contraindicated. It is my opinion and has been my experience that infantile eczema always responds quite satisfactorily to other forms of treatment. Psoriasis may show a mild temporary improvement with steroid therapy. However, it is short-lived, and the skin lesions become worse when administration of the drug is discontinued. Steroids should be used only in cases in which psoriasis has progressed or appears to be progressing to exfoliative dermatitis. Steroids should not be administered systemically in most cases of contact dermatitis. The exception to this statement would be severe generalized contact dermatitis that is associated with a considerable amount of discomfort. In this case, administering a steroid will produce symptomatic relief, but it will have little effect on the course of the disease.

Conclusion

Dermatology is by no means the obscure and mysterious branch of medicine which it is considered to be by many physicians. Such a misconception is the result of inadequate time devoted to its teaching in both medical school and internship. It is the dermatologist's hope that other physicians will come to recognize it as a stimulating, interesting and nonobscure part of medical practice. Great strides toward this goal may be made by dispelling the fables and fallacies which becloud understanding of the skin and its diseases. It is my sincere hope that this presentation has been of some value in this respect.

Postgraduate Clinical NOTES

125. RESISTANCE TO CEREBRAL ANOXIA IN CHILDREN

The question arises how long the immature nervous system in man can tolerate anoxia without irreversible damage. It is probable that the newborn and infant brain is more resistant to anoxia than the adult brain. In the human adult it is generally conceded that cardiac arrest cannot be tolerated for longer than four minutes without irreversible brain damage. It appears that any resistance of the immature brain to anoxia is soon lost, however, for at the age of four years the critical period for cerebral anoxia is similar to that of the adult. We have recently examined a child aged four years who had suffered from cardiac arrest for seven minutes during a tonsillectomy. As a result of this brief episode of ischemic anoxia, the child remained totally decerebrate for two weeks at which time death supervened without any sign of neurological improvement.

John S. Meyer, Changing concepts in childhood neurology, *Medical Times*, June 1959, pp. 743-760

Macroglobulinemia of Waldenström

CLINICAL, LABORATORY AND ANATOMIC FEATURES

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In macroglobulinemia of Waldenström, there appears to be a questionably malignant involvement of the lymphatic reticuloendothelial system which causes bleeding, anemia and infections. The etiology is unknown and the outcome is eventually fatal. Various clinical features and laboratory findings help to differentiate this disease from multiple myeloma, chronic lymphatic leukemia, lymphosarcoma and purpura hyperglobulinemia.

Treatment is symptomatic, consisting of blood transfusions and administration of adrenocortical steroids and adrenocorticotropic hormones.

M. RICHARD PACHTER

As of 1959 there existed in the world's literature approximately 150 cases that met the criteria for a diagnosis of macroglobulinemia of Waldenström, a disease of unknown etiology. Although this syndrome has received extensive consideration in the European literature since it originally was reported in 1944,[1] a distinct paucity of subsequent reports exists in American journals.[2] This condition is of interest not only because of its relative rarity but also because of the difficulty in differentiating it from multiple myeloma, chronic lymphatic leukemia, lymphosarcoma and purpura hyperglobulinemia.

Clinical Features

General—Although the Swiss authors[3] divided their cases of macroglobulinemia of Waldenström into benign and malignant varieties on the basis of the severity of symptoms and the natural history of the disease, others have been unable to corroborate the large number of malignant cases noted by the former. However, in the Swiss studies the numerically superior patients with malignant disease demonstrated a 30 month course from time of the first symptom to time of death and a 16

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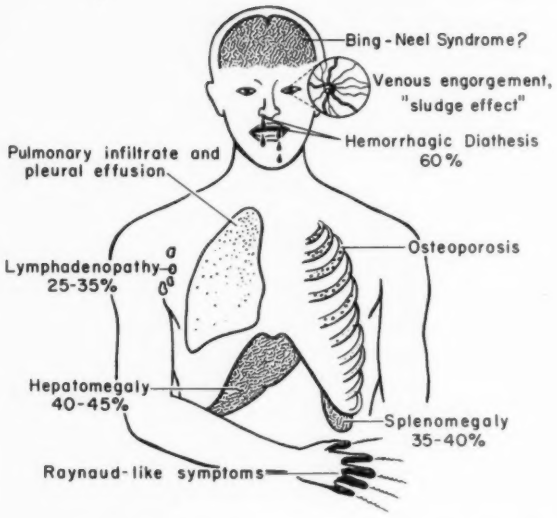


FIGURE 1. Schematic presentation of the most frequently observed clinical findings in macroglobulinemia of Waldenström. Any of the noted phenomena may be absent in a given case.

month span from time of diagnosis to death, compared with 67 and 31 month periods, respectively, for the patients with benign disease.

The majority of the reported cases (about 80 per cent) have been in persons more than 50 years of age, with a male-to-female ratio of approximately 2.5 to 1. Occasionally, the disease has been noted in people less than 40 years of age, but it has not been reported in children, adolescents or young adults.

When first seen, the patients usually present a nonspecific picture of anorexia, weight loss, general malaise, frequent infections and a bleeding tendency. Bleeding usually occurs in the form of hemorrhage from the mucous membranes, i.e., epistaxis, gingival bleeding or, less commonly, retinal, vaginal or gastrointestinal hemorrhage. Approximately 30 per cent of patients have localized, painless, moderate-sized lymphadenopathy; 40 per cent have mild to moderate painless splenomegaly, and 45 per cent have mild to moderate hepatomegaly (figure 1).

Special systems—A Raynaudlike acrocyanosis as the result of the concomitant presence of cryoglobulins or the increased viscosity of the blood, due to the presence of undue amounts of macroglobulins, is infrequently found.

The retinal and conjunctival vessels of the sclerae may reveal arterial narrowing, dilatation of veins, stasis of blood flow, and beadlike clumping of blood elements (figure 2). On occasion, the eyeground[3] may also demonstrate punctate or linear hemorrhages, and cases of amblyopia, retinal detachment and thrombosis of the central vein are recorded in the literature.[4]

Bone surveys often reveal a moderate osteoporosis, usually of the spinal column, but only rarely are there extensive osteolytic foci such as those seen in multiple myeloma.[5] Usually, no abnormal chemistry values are found in the blood, although an exceptionally rare case with hypercalcemia or increased alkaline phosphatase has been reported. Occasionally, there is marked decrease in total serum lipids.

Neurologic symptoms in the form of vertigo, polyneuritis, sensory disturbances, eighth nerve affliction, psycho-organic syndromes, transitory aphasia and tremors have been noted in conjunction with macroglobulinemia of Waldenström. These signs and symptoms are not a consistent or diagnostic part of the clinical picture, and the previous association with the Bing-Neel syndrome (paresis of the lower extremity, optic neuritis, and a positive Babinski sign) has not been adequately substantiated. Most of the neurologic phenomena can be explained on the basis of focal hemorrhage, age of the patient, and the state of the vascular tree. In the few cases in which the cerebrospinal fluid has been evaluated, normal values, increased albumin and macroglobulins have been reported.[6]

On very rare occasions miliary infiltrates of the lungs, with and without pleural effusions, have been described. In 10 per cent of the reported cases of macroglobulinemia of Waldenström there has been an associated carcinoma, but the cause-and-effect relationship remains obscure.

Laboratory Examinations

Hemogram—Due to the presence of increased macroglobulins the blood shows a

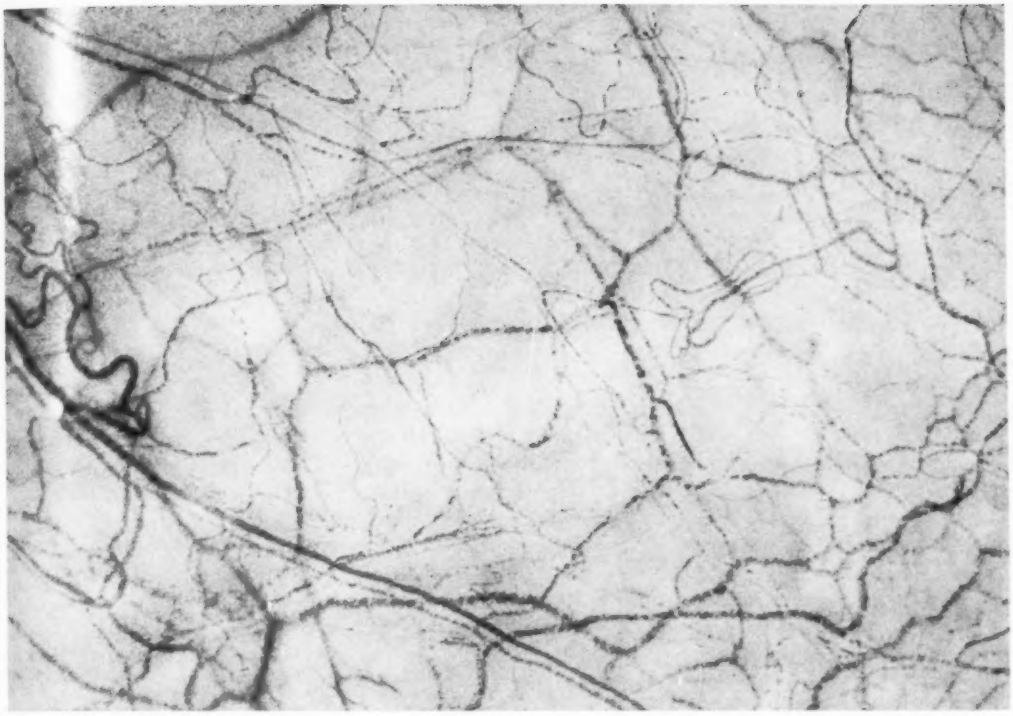


FIGURE 2. Photograph of scleral conjunctival vessels from a patient with macroglobulinemia of Waldenström demonstrating beadlike clumping of cellular elements. x 100.

markedly enhanced viscosity, and the erythrocyte sedimentation rate is frequently over 100 mm. in one hour. Both findings are useful in differentiating the syndrome from leukemia and lymphosarcoma. There is usually a normochromic or microcytic hypochromic anemia of moderate to marked degree. This probably results from the summation of hemorrhage, replacement of marrow, and, perhaps, coating of the erythrocytes by macroglobulins, with increased aggregation and resultant mechanical shattering caused by passage through the terminal vascular bed. Some reports of hemolytic anemia have been presented in which partial and complete warm antibodies, as well as auto-agglutinins, have been demonstrated.[7]

The white blood cell picture is generally nonspecific, although instances of mild lymphocytosis, leukocytosis and leukopenia have been recorded. Only in exceptionally rare cases have the supposedly pathognomonic lymphoid-reticulum cells been found in the peripheral blood.[8]

In the largest series of cases reported in which the marrow has been evaluated, a picture interpreted as typical was described.[3] There is a focal or diffuse infiltration by varying numbers of small or large lymphoid-reticulum cells and typical and atypical plasma cells (figure 3). The former cells, as contrasted with lymphocytes, have a deeper blue cytoplasm and a less homogeneous chromatin pattern and frequently present one or more nucleoli. The increased number of mast cells[9] and fibrocytelike cellular elements also has been emphasized. In a given case in which the infiltration is focal or the disease is in its ascendancy, a single marrow aspiration may be totally unremarkable. At present, staining procedures are being performed on bone marrows of healthy persons and patients with macroglobulinemia as well as other diseases.

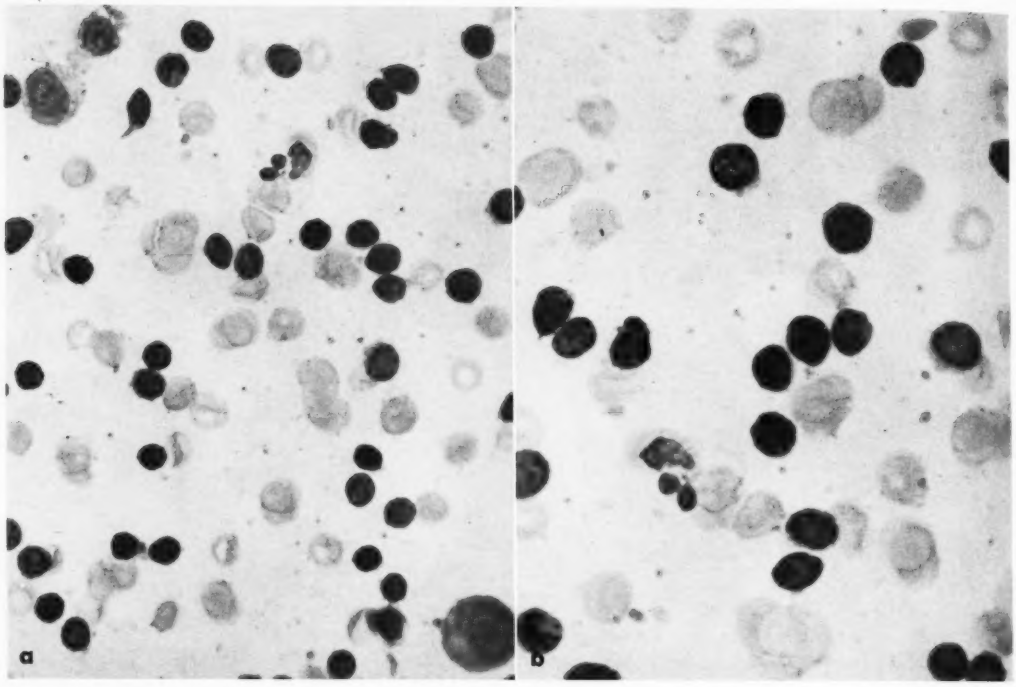
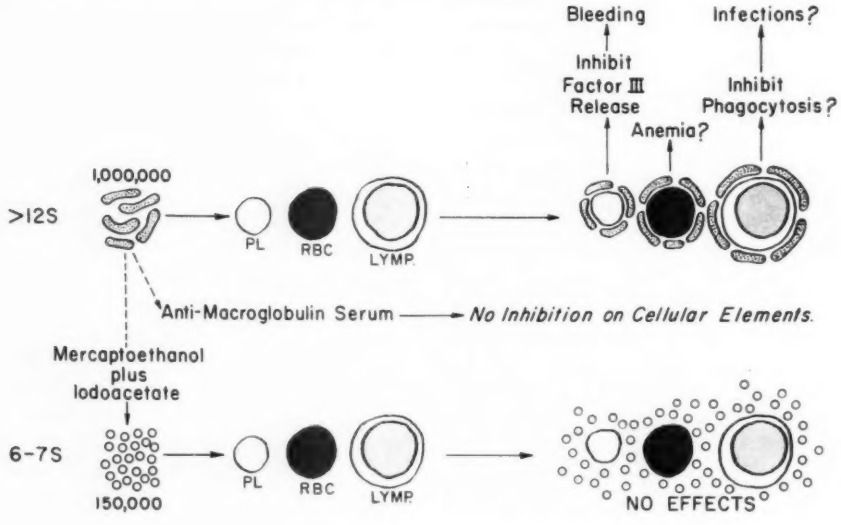


FIGURE 3a. Sternal marrow showing a diffuse involvement with lymphoid cells and occasional plasma cells. x 720. b. Diffuse involvement with lymphoid cells. x 1,080.

FIGURE 4. Schematic presentation of the pathogenesis of the hemorrhagic diathesis. The dissociation units of the macroglobulins, as averse to the intact molecule, have no deleterious effect.



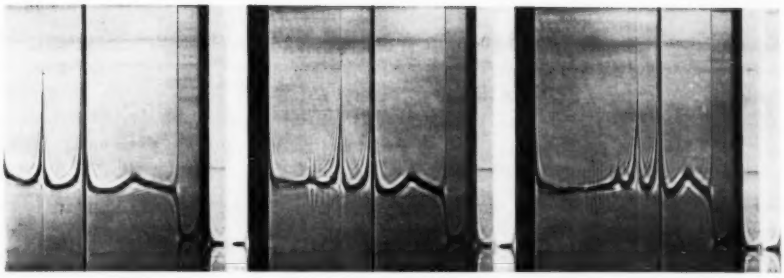


FIGURE 5. Typical electrophoretic pattern seen in macroglobulinemia of Waldenström. A similar tall, narrow and small-based peak may be observed in multiple myeloma, atypical leukemia and occasional cases of idiopathic hyperglobulinemia.

Fluorescein isocyanate-tagged rabbit anti-macroglobulin serum is used to evaluate the specificity of fluorescence in the various situations. Should a definitive and objective difference be noted, a relatively reliable screening test may be evolved.

Many factors, from afibrinogenemia to a deficiency of factor VII, have been implicated in the hemorrhagic diathesis, but no common denominator has been established. Recent work has proposed that the basic deficiency lies in a mechanical blockade of the platelet surface by macroglobulins, with the subsequent prevention of the release of platelet factor III (figure 4). In our cases, the presence of a prolonged bleeding time and short prothrombin consumption time and the lack of residual prothrombin in the serum are highly indicative of a platelet aberration.[10] This external interference may be accompanied by alteration of the platelet membrane, with entrance of macroglobulin into the platelet and a subsequent deleterious effect on the thereincontained granules.

Proteins—The total protein varies from 7.5 to over 12 gm. per cent, with the macroglobulins constituting 20 to 50 per cent of the noted paraproteins (abnormal proteins noted in multiple myeloma, macroglobulinemia of Waldenström, and occasional leukemias). Approximately 50 per cent of reported cases reveal a hypoalbuminemia. The electrophoretic pattern reveals a tall, narrow, small-based peak most commonly in the gamma or beta-2 fraction although it has been noted in the alpha and beta-1 areas (figure 5). Starch electrophoresis has been reported as being useful in the differential diagnosis of multiple myeloma. In this situation the proteins found in myeloma migrate like normal globulins, whereas the macroglobulins fail to wander.[11] On occasion, electrophoresis performed on urine has given patterns similar to those of serum. Bence Jones

FIGURE 6. Macroglobulin at a concentration of 1.7 gm. per cent in 0.2 M sodium chloride, studied in a Spinco Model E ultracentrifuge operating at a speed of 52,640 rpm. The photograph was taken 19 minutes after the ultracentrifuge reached the specified speed. Three macroglobulin components (305, 245 and 1,651) are present in the pattern.

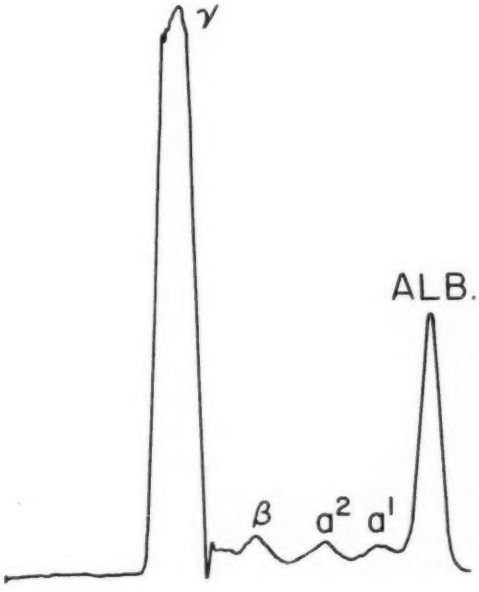


TABLE 1

MAJOR CRITERIA USED IN DIFFERENTIAL DIAGNOSIS OF MACROGLOBULINEMIA OF WALDENSTRÖM

CONDITION	LIVER	SPLEEN	LYMPH NODES	BONE	ELECTROPHORESIS
Macroglobulinemia of Waldenström	++	++	++	Osteoporosis	Hyperglobulinemia with tall, narrow, small-based peak
Multiple myeloma	±	±	±	Osteolytic lesions	Hyperglobulinemia with tall, narrow, small-based peak
Chronic lymphocytic leukemia	+	++	+++	Tumor, osteolytic, subperiosteal	Nonspecific
Lymphosarcoma	+	++	++++	Osteolytic lesions	Nonspecific
Purpura hyperglobulinemia	±	±	±	Absent	Hyperglobulinemia with broad-based peak

KEY:

± = negligible, rarely
\+ = mild
++ = moderate
+++ = marked
++++ = very marked

protein has been found in an occasional case of macroglobulinemia. Cryoglobulins are occasionally encountered, but their presence is not typical.

Ultracentrifuge studies reveal the presence of over 4 per cent (normal value) of proteins, with a sedimentation constant (S) of at least 12 S and a molecular weight of about 1,000,000. The macroglobulins occasionally found in myeloma are usually under 12 S (figure 6). The macroglobulins also frequently present a very high content of carbohydrates, as evidenced by electrophoretic strips stained with PAS. Secondary increase in macroglobulins has been reported in nephrosis, liver diseases, lupus erythematosus, periarteritis nodosa, congenital syphilis, etc., but never has it occurred with the consistency and clinical pattern noted in macroglobulinemia of Waldenström.

The Sia water test, in which distilled water is added to the patient's serum in a 20 to 1 ratio, with resultant heavy and rapid formation of a white precipitate, has proved nonspecific due to the presence of many known false positive and negative reactions. On the other hand, results of the formol-gel test, although positive in other conditions, have very rarely proved to be negative in the presence of macroglobulins.

Immunochemistry—Rabbit antibodies produced against macroglobulins have been reported as being specific not only for the given antigen but also for the macroglobulin in a given patient. This test is carried out using the rabbit antimacroglobulin serum against the patient's serum in the form of a ring precipitin test. Patients with macroglobulinemia of Waldenström[11] have very high precipitin titers in comparison with healthy persons or with patients who have myeloma or any of the other conditions in which an increase in macroglobulins is secondary to another disease process.[12]

It has recently been suggested that pathologic macroglobulins may be differentiated from normally occurring ones by means of the effect of dissociation of the native molecule on viscosity. The pathologic macroglobulins would dissociate and reveal a lessened viscosity, while the others would not be affected and would reveal their initial viscosity.

Histopathology—Zollinger[13] very extensively evaluated the histopathologic features in this syndrome and believes that in experienced hands the cytology may be diagnostic. A focal or diffuse infiltrate always is present in the bone marrow; it is often found in the lymph nodes, and occasionally is seen in the spleen, liver and other organs. The infiltrate is composed of lymphoid-reticulum cells, typical and atypical plasma cells and mast cells in

TABLE 1 *(Continued)*

MAJOR CRITERIA USED IN DIFFERENTIAL DIAGNOSIS OF MACROGLOBULINEMIA OF WALDENSTRÖM

ULTRACENTRIFUGE	PERIPHERAL BLOOD	IMMUNOCHEMISTRY	COAGULATION	MARROW
Always above 5 per cent macroglobulins	Rarely involved	Positive	Primarily platelet aberration	Lymphoid-reticulum cells, typical and atypical plasma cells
Rarely above 5 per cent macroglobulins	Rarely plasma cells	Negative	Multiple etiology	Myeloma cells
Rarely above 5 per cent macroglobulins	Typical cells	Negative	Multiple etiology	Leukemic infiltrate
Rarely above 5 per cent macroglobulins	Nonspecific	Negative	Multiple etiology	May be normal or reveal atypical cells
Rarely above 5 per cent macroglobulins	Nonspecific	Negative	Multiple etiology	Nonspecific

varying proportions. The findings in the lymph nodes may simulate a lymphoma very closely, but there is not the complete obliteration and monotony of cell type seen in leukemia and lymphosarcoma. It is also pointed out that the transitional forms of lymphoid-reticulum cells to plasma cells are peculiar to macroglobulinemia. Renal, cardiac and central nervous system involvement is noted, but not with the specificity and the regularity seen in other organs.

Summary

An attempt has been made to present adequately the clinical and laboratory features of macroglobulinemia of Waldenström in a manner that would be helpful in differentiating this disease from multiple myeloma, lymphatic leukemia, lymphosarcoma and purpura hyperglobulinemia (table 1). The etiology is unknown; the therapy is symptomatic (blood transfusions, adrenocortical steroids, adrenocorticotropic hormones), and the outcome is eventually fatal. The syndrome would appear to be a questionably malignant involvement of the lymphatic reticuloendothelial system in which the increased amounts of macroglobulins present may deleteriously affect platelets, erythrocytes and leukocytes, with resultant bleeding, anemia and infections.

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Hemoptysis as an Indication for Surgical Treatment of Bronchiectasis in the Aged

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Pulmonary hemorrhage in an elderly patient who previously has had tuberculosis more likely indicates bronchiectasis than a relapse of tuberculosis.

Diagnostic procedures should include an x-ray of the chest, examination of sputum, hematologic studies, and bronchoscopy.

If the source of bleeding can be determined, resection is advisable after a single major recurrence.

ALFRED S. FROBESE

Two decades ago bronchiectasis had a poor prognosis.[1] The principal manifestations in severe cases were cough, foul sputum, recurrent pneumonia, pulmonary abscess and metastatic brain abscess. Hemoptysis was a frequent symptom but usually of secondary importance. With the advent of antibiotic drugs and the development of surgical resection, the prognosis has been strikingly improved. Cough, foul expectoration and recurrent pneumonia have been reduced to relatively minor proportions. The improved outlook for patients receiving medical therapy and the slightly increased hazard of thoracic surgery in the older patient have given support to the belief that surgery for bronchiectasis is seldom indicated in older patients. In a recent investigation on bronchiectasis in the older patient, Pittman[2] stated that this was essentially a medical problem.

Effective as the antibiotics have been in suppressing infection, they have not solved the problem of bleeding in bronchiectasis. Hemorrhage now threatens to become the chief indication for operation in this disease.

Case Reports

The histories of four elderly women in whom repeated pulmonary hemorrhage developed as a result of bronchiectasis are briefly presented. The onset of bleeding occurred in three patients 20 or more years after recovery from pulmonary tuberculosis; one of these

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patients had had thoracoplasty. The fourth patient had cystic bronchiectasis which also may have been tuberculous in origin. It should be emphasized that in none of these patients did the bleeding occur as the result of relapse of tuberculosis.

Case 1—A 60 year old white woman was admitted to the Graduate Hospital of the University of Pennsylvania in March 1952 for elective pulmonary resection. From 1920 to 1926, she was in a sanatorium for treatment of advanced tuberculosis of the right lung. In 1926, a thoracoplasty of the right side was performed, and sputum examinations were subsequently negative. She was well until 1947, at which time pulmonary hemorrhage occurred, persisting for 11 days. Although her sputum was still negative, further collapse of the right lung by a more extensive thoracoplasty was accomplished. Nevertheless, recurrent pulmonary hemorrhage resumed in 1948. An x-ray of the chest on admission to the hospital in 1952 showed extensive collapse of the right lung. Sputum was negative for acid-fast bacilli, and no lesion could be identified at bronchoscopy. Moderate cylindric bronchiectasis in the collapsed right lung was demonstrated by bronchography (figure 1), and a pneumonectomy of the right lung was performed. The excised lung showed healed tuberculosis and post-tuberculous or post-thoracoplasty bronchiectasis (figure 2). Recovery from surgery was uneventful, and the patient has had no further episodes of bleeding or respiratory symptoms.

Comment—Bronchiectasis rather than active tuberculosis was presumably responsible for the hemorrhages beginning in 1947. Resection rather than additional thoracoplasty should have been performed; the former procedure undoubtedly would have been elected had a bronchogram been done at the time.

Case 2—A 66 year old white woman was admitted to the Graduate Hospital for the fourth time in May 1956 because of severe hemorrhage of 12 hours' duration.

Following treatment for cavitary tuberculosis of the upper lobe of the left lung in 1934, her only respiratory symptoms were five minor episodes of pulmonary hemorrhage between 1934 and 1942. A more severe episode of bleeding led to hospitalization in 1952. In 1954, she was admitted to the hospital in congestive failure and was subsequently maintained on digitalis and a low salt diet. In 1955, bleeding episodes became more severe and more frequent; she was hospitalized in March 1956 and again in May 1956.

X-rays of the chest revealed fibrosis and calcifications indicative of healed tuberculosis in the apex of the left lung (figure 3). Bronchiectasis was suspected, but bronchograms failed to demonstrate diagnostic changes. In view of the cardiovascular disease and the patient's age, surgery was not seriously considered at this time, and the patient was discharged to a convalescent home on May 16, 1956. On May 18, 1956, profuse hemorrhage began, and the patient was returned to the hospital.

Bleeding continued in amounts of several cupfuls at irregular intervals throughout the day. On admission to the hospital the patient's hemoglobin level was 9 gm. per 100 cc., although it had been 12.3 gm. per 100 cc. a week earlier. Bronchoscopy was carried out when bleeding appeared to have slowed. Blood was seen throughout the bronchial system of the left lung, but the greatest amount was emerging from the bronchus of the upper lobe. There was no indication that the bleeding was subsiding, and it was reasoned that heart-failure was caused by loss of blood. Accordingly, the patient was rapidly prepared for surgery by digitalization and blood transfusions, and a lobectomy of the upper lobe of the left lung was carried out as an emergency procedure. The operative specimen demonstrated marked

FIGURE 1 (case 1). Preoperative bronchogram made in 1952.

FIGURE 2 (case 1). Resected right lung showing extensive fibrosis and bronchiectasis.

bronchiectasis. Convalescence was prolonged as the result of congestive failure, but the patient is now well and has had no further pulmonary bleeding.

Comment—This case exemplifies the recurrent and progressive nature of this type of bleeding. Emergency resection might have been avoided had it been recognized earlier that surgery was inevitable.

Case 3—A 60 year old white woman was admitted to the Graduate Hospital in January 1957 because of severe hemoptysis. She stated that she had expectorated several cupfuls of blood. She had been hospitalized in 1953 for pneumonitis of the upper lobe of the right lung. At that time, roentgenograms showed tuberculosis at the apex of the right lung and cystic changes which were suggestive of bronchiectasis in the upper lobe of the right lung (figure 4). In 1955, the patient was again hospitalized for pneumonitis; at that time a bronchogram demonstrated bronchiectasis of the upper lobe as well as changes in the middle lobe. In 1956, an initial severe pulmonary

FIGURE 3 (case 2). Roentgenogram showing fibrocalcific disease of the upper lobe of the left lung.

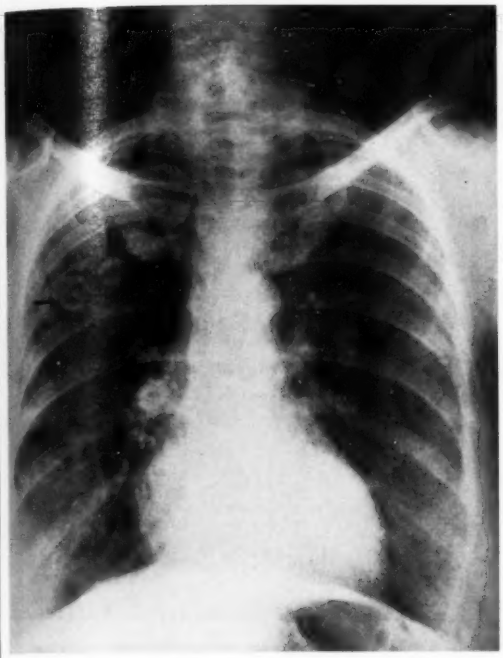


FIGURE 4 (case 3). Roentgenogram showing cystic bronchiectasis of the upper lobe of the right lung.

hemorrhage occurred which led to hospitalization. Bleeding subsided with conservative management. Despite continued administration of antibiotics, bleeding recurred several months later and resulted in readmission.

The bleeding again subsided, and bronchoscopic examination was carried out. Old blood and secretions were noted in the bronchus of the lower lobe of the left lung, and bilateral basilar bronchiectasis was suspected. This was at variance with the bronchographic findings. While receiving antibiotic therapy in the hospital, the patient had two additional hemorrhages amounting to 8 oz. of blood each. Thoracotomy was performed, and a lobectomy of the upper and middle lobes of the right lung was done. The findings in the surgical specimen concurred with those of the bronchograms. The patient's postoperative course was smooth, and no further bleeding has occurred.

Comment—The failure of antibiotic drugs to prevent hemorrhage and the fallibility of bronchoscopy in determining the source of pulmonary bleeding are shown in this case.

Case 4—A 59 year old white woman was first admitted to the Graduate Hospital in September 1957 because of recurrent pulmonary hemorrhage. The inception of the bleeding was in 1949, but the first episode which was sufficiently severe to require hospitalization occurred in 1955. Calcifications of the apex of the right lung, shown in x-rays of the chest for many years, were presumed to be a healed tuberculous lesion. In 1956, the patient had been again hospitalized because of pulmonary hemorrhage amounting to a glassful of blood per day for five days. A roentgenogram at this time (figure 5) showed a density in the superior segment of the lower lobe of the left lung; this was interpreted as a tumor, an interlobar effusion or segmental atelectasis. This shadow disappeared in one week. Bronchoscopic examination on two occasions failed to reveal a cause for the hemorrhages.

Immediately prior to admission to the Graduate Hospital, the patient had expectorated 1.5 pt. of blood, and her hemoglobin had fallen to 10 gm. per 100 cc. Bleeding subsided while she was in the hospital. A bronchogram showed cystic bronchiectatic areas in the superior segment of the lower lobe of the left lung and the lingula (figure 6). At thoracotomy, the superior segment of the lower lobe of the left lung and the lingula were resected. Examination of the surgical specimen showed marked bronchiectatic changes (figure 7). Convalescence was prolonged due to staphylococcal empyema, but the patient is now well and to date has had no further hemoptysis.

Comment—In retrospect, it seems likely that the roentgenographic density noted in 1956 represented atelectasis due to aspiration of blood in the affected segment. This case demonstrates the value of bronchograms even though repeated bronchoscopy shows negative findings.

Discussion

The pathogenesis of bleeding in bronchiectasis has been described by Liebow, Hales and Lindskog.[3] These investigators have emphasized the importance of enlargement of the bronchial arteries in the diseased area. Dilated and tortuous bronchial arteries anasto-

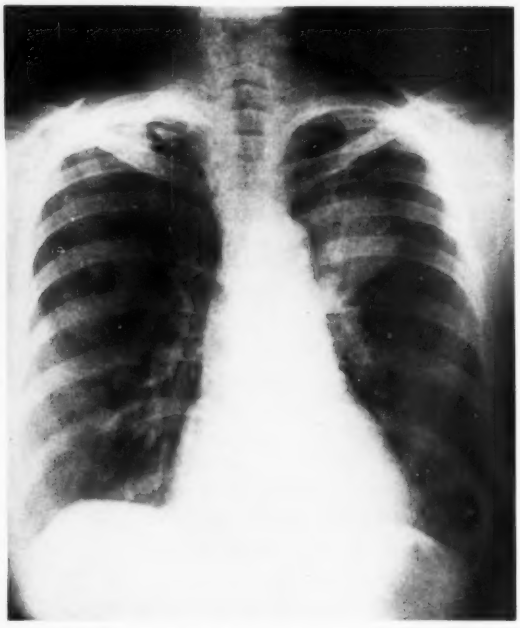


FIGURE 5 (case 4). Roentgenogram made on August 5, 1956, showing density in the lower lobe of the left lung, which was interpreted as a tumor. This density disappeared in a week. It evidently represented atelectasis of the superior segment of the lower lobe due to occlusion of the bronchus by blood.

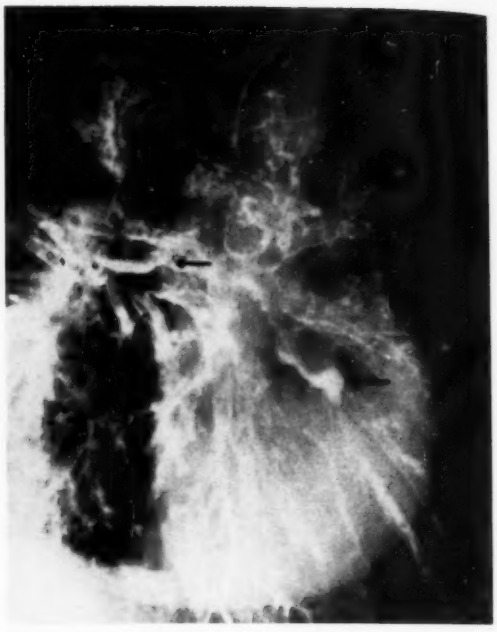
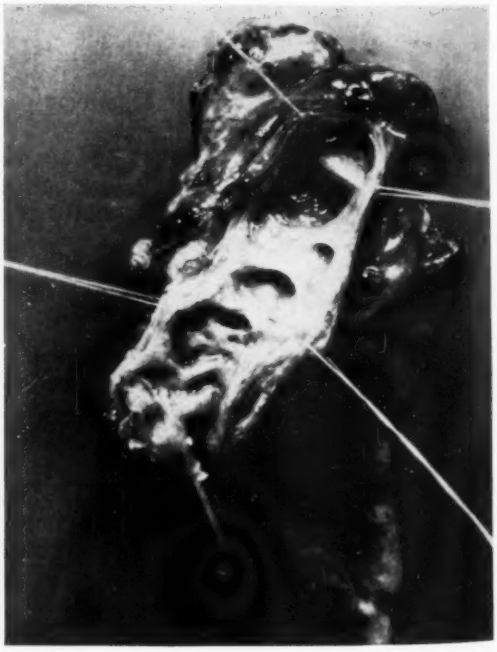


FIGURE 6 (case 4). Projection of bronchogram showing cystic bronchiectasis of the superior segment of the lower lobe and lingula.

FIGURE 7 (case 4). Surgical specimen showing marked cystic bronchiectasis.



mose with the pulmonary arterial system, thereby effecting a left-to-right vascular shunt. In the young patient with bronchiectasis of brief duration, hemoptysis is apt to be minimal. Bleeding of greater magnitude is usually the result of abscess. In bronchiectasis of longer duration, occurring in older patients, there has been time for a gradual expansion of the bronchial artery-pulmonary artery anastomoses. If bleeding occurs under these circumstances, it may be very severe, amounting to several hundred cubic centimeters.

Bronchiectasis is a common sequela of healing of pulmonary tuberculosis.[4] Contracture of the fibrotic scar exerts traction on bronchi and bronchioles which have been damaged by tuberculosis. Bronchiectatic lesions of this type are most often encountered in the usual sites of tuberculosis, namely, the upper lobes and the apexes of the lower lobes. This is in contrast to the basal location of idiopathic bronchiectasis. Furthermore, post-tuberculous bron-

chiectasis is more often peripheral in location, and the central bronchi tend to be normal in caliber and structure. It is presumably the apical localization of post-tuberculous bronchiectasis which distinguishes its clinical manifestations from those of basal bronchiectasis. In the latter, accumulation of secretions and suppuration with recurrent pneumonitis are characteristic; in the former, as a result of better drainage of secretions, dry bronchiectasis is more often noted. In this form there may be few symptoms except bleeding.

Post-tuberculous bronchiectasis is by no means uncommon in patients who survived tuberculosis in the era prior to chemotherapy. Such bronchiectatic changes may paradoxically prove to be more frequent in the future, since with modern therapy survival is almost universal.

From the experience reviewed here, it is evident that when an elderly patient with a history of treatment for tuberculosis or with roentgenographic evidence of healed tuberculosis has a brisk pulmonary hemorrhage, the source is more likely to be bronchiectasis than tuberculosis. Appropriate studies include a roentgenogram of the chest and examination of the sputum to exclude reactivation of tuberculosis, bronchography, and hematologic studies to exclude defects in coagulation of the blood. Bronchoscopy should be done to exclude a centrally located neoplasm, even though profuse bleeding of this nature is not characteristic of tumor. As Ehrenhaft and Taber[5] have pointed out, the value of bronchoscopy is related to the presence of active bleeding at the time of the examination. If the hemorrhage is active, the endoscopist should be able to identify the area from which the blood is coming. In our experience, bloody secretions found in the bronchi after bleeding has ceased actually may mislead the examiner as to the site of origin. Bronchography is certainly a requisite to a complete work-up. Post-tuberculous bronchiectasis in the apexes of the upper lobes is in some patients difficult to demonstrate, but bronchographic mapping is essential to planned segmental pulmonary resections.

If the source of bleeding can be demonstrated, we believe that resection is indicated after a single recurrence. Once bouts of bleeding have started, it is evident that they tend to recur with increasing frequency and severity. Procrastination because of a patient's age may result in an emergency operation when the patient is less able to withstand surgery because of loss of blood or because of aspiration pneumonitis.

Summary

1. Four instances are reported of post-tuberculous bronchiectasis in elderly patients in whom surgical resection was required because of recurrent pulmonary hemorrhage.

2. Post-tuberculous bronchiectasis is characterized by recurrent hemoptysis, which tends to increase in severity with age.

3. If the source of bleeding can be demonstrated, resection is advisable after a single major recurrence.

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Meralgia Paresthetica

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Meralgia paresthetica occurs frequently and should be differentiated from paresthesias caused by derangements of the lower back. Three cases are presented in which patients had paresthesias and anesthesia over the distribution of the lateral femoral cutaneous nerve after wearing some encircling apparatus such as a pelvic belt. Unwarranted surgery will be avoided by correct diagnosis and treatment of meralgia paresthetica.

LEWIS COZEN

MERALGIA paresthetica is an affection of the lateral femoral cutaneous nerve. The symptoms are numbness and paresthesia along the distribution of the nerve on the outer side of the thigh. Although the exact cause of this affection has never been determined, it has been surmised that it may be due to excessive fat along the course of the nerve or to pressure by a belt over the rim of the pelvis. Stevens[1] recently has written an excellent summary of this "minor neurologic problem," and he has stressed its frequency.

In cases which I have observed, meralgia paresthetica has developed after the patients had worn an apparatus which seemed to cause pressure on the lateral femoral cutaneous nerve as it crossed the brim of the pelvis. Since the patients in these cases had pain in the back, it could readily be assumed that the paresthesia arose from the spinal column. If this erroneous assumption is made, the treatment and prognosis might vary a great deal.

Ecker[2] noted that meralgia paresthetica developed after adhesive strapping had been applied to the lower part of the back and after patients had worn a sacro-iliac belt.

Case Reports

Case 1—Pain developed in the left leg of a 64 year old man after he had sustained a twisting injury of his back. After he had worn a canvas lumbosacral belt for two weeks, he complained of numbness and paresthesia of the lateral aspect of the right thigh. Examination by me revealed anesthesia along the distribution of the lateral femoral cutaneous nerve

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on the lateral aspect of the right thigh. The patient was advised to discontinue the use of the belt. The result could not be ascertained because he did not return for examination.

Case 2—A 70 year old woman sustained a fracture of the ischium and pubis. Because of continued discomfort in the groin, a pelvic type of traction was applied, and 20 lb. of weight was used. Three days after the traction was applied, the patient complained of numbness and paresthesia of the outer part of the left thigh. Examination disclosed anesthesia to pin prick in the area of distribution of the lateral femoral cutaneous nerve. After the anterior rim of the ilium was anesthetized with 15 cc. of a 1 per cent solution of XYLOCAINE®, the paresthesia disappeared. Two days after the use of the pelvic belt and traction was discontinued, all disturbances of sensation in the thigh disappeared.

Case 3—Pain that was typical of a ruptured intervertebral disk developed in the back and left leg of a 34 year old man. The pain was so severe that it was necessary to hospitalize the patient. Pelvic traction was applied, and 20 lb. of weight was used. Five days after application of the traction, the patient noted tingling and "a peculiar feeling of the right thigh." Examination revealed paresthesia and anesthesia along the distribution of the lateral femoral cutaneous nerve on the outer aspect of the thigh. The traction was maintained for another five days because of the severity of the pain. The paresthesia and anesthesia continued for two months, and then disappeared.

Comment

I know of several other cases in which numbness and paresthesia developed over the outer aspect of the thigh after the application of a brace, belt or pelvic traction. I do not have the clinical details in these cases, but the history was similar to that obtained in the three cases which I have reported.

In cases in which numbness and tingling develop after onset of pain in the lower part of the back or in the leg, the paresthesia easily may be misconstrued as originating in the spinal column. If the true cause of the paresthesia is not recognized, an unwarranted operation may be performed and the prognosis may be poor.

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Insulinoma of the Pancreas

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Hypoglycemia resulting from islet cell tumor of the pancreas necessitates prompt diagnosis and treatment. The diverse clinical manifestations are caused by a low concentration of blood sugar. Determining the value for the fasting blood sugar is probably the most useful diagnostic test. A case is reported in which intravenous administration of REGITINE® *proved of diagnostic value. Use of the test is suggested when the presence of islet cell tumor is suspected.*

HYPOGLYCEMIA resulting from an islet cell tumor of the pancreas was first recognized as a clinical entity by Wilder, Allan, Power and Robertson[1] in 1927. In the case which they reported, the clinical diagnosis was confirmed by the removal of an islet cell carcinoma. The diverse clinical manifestations are due to a low concentration of blood sugar. The most common symptoms are fatigue, lassitude, restlessness, tremor of the hands, sweating, hunger, weakness, irritability, anxiety, numbness, palpitation, craving for sweets, fainting and, at times, convulsions.

CLORINDA SCARPA-SMITH

The dangerous consequences of hypoglycemia necessitate prompt diagnosis and treatment. Irreversible injury of the brain may occur after severe hypoglycemia, i.e., a concentration of less than 20 mg. of sugar per 100 cc. of blood, has been present for only three minutes. Convulsions are likely to occur when the concentration of blood sugar decreases to this level.[2,3] Signs and symptoms usually appear when the concentration of blood sugar decreases to 50 mg or less per 100 cc., although some patients become accustomed to this low concentration.[4-7]

Severe and progressive hypoglycemia is usually associated with hyperinsulinism, which is due either to a tumor of the cells of the islets of Langerhans or to diffuse pancreatic hyperplasia.[3] The incidence of hypoglycemia (both functional and organic) seems to be about the same as that of diabetes mellitus.[8] Landmann and Sutherland[9] found that 44 per cent of 50 consecutive patients who were admitted to the Psychosomatic Appraisal Unit of

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the Winter Veterans Administration Hospital had hypoglycemia. Ten per cent of the cases of hypoglycemia could be classified as cases of organic hyperinsulinism.

Organic hyperinsulinism may be caused by diffuse hypertrophy or hyperplasia of the islets of Langerhans, islet cell adenoma, islet cell carcinoma, adrenocortical insufficiency, hypopituitarism, hypothyroidism, lesions of the central nervous system (hypothalamus), disease of the liver, fibroma or sarcoma.[3]

The incidence of hyperinsulinism due to islet cell tumor is about equal in the two sexes. It may occur at any age, from the neonatal period onward, but it most frequently occurs in persons who are between 35 and 60 years of age.[10] When this disease occurs in younger persons, the symptoms are more severe, and the disease may be mistaken for epilepsy.

Organic hyperinsulinism is not easy to distinguish from functional hypoglycemia.[2, 4, 11-15] There are a few signs and symptoms that will be helpful in making the differential diagnosis. In 1938, Whipple[16] formulated a triad that is requisite for the diagnosis of an islet cell tumor. This triad includes a history of attacks of hypoglycemia that occur in the fasting state, a blood sugar concentration of less than 50 mg. per 100 cc. during the attacks, and relief of the symptoms by the administration of glucose. This triad is still used in the diagnosis of this tumor.

An islet cell tumor behaves like any other tumor; i.e., it usually is progressive and is manifested by a gradual increase in the frequency and severity of the attacks. Furthermore, release of the insulin that is produced is not subject to the usual regulatory mechanisms for the control of the concentration of blood sugar. For this reason, the attacks usually occur at night or before breakfast, and they may be precipitated easily by a period of fasting. Unlike the attacks of functional hypoglycemia, they are unrelated to emotional or environmental situations or to meals, except that hunger is always present and there is an intolerance to fasting.

Determination of the value for the fasting blood sugar probably is the most valuable test for the presence of this disease. If the fast is extended for 24 to 48 hours, clinical signs and symptoms of hypoglycemia will become evident, and the concentration of blood sugar will drop below 50 mg. per 100 cc. This decrease is diagnostically significant. The glucose tolerance test is of value only if the patient has been adequately prepared for the test. For a minimal period of at least three days, the daily diet should include at least 150 gm. of carbohydrate.[17] Thus, the amount of glycogen stored in the liver ordinarily would be sufficient to maintain the concentration of blood sugar at a normal level. However, if the concentration is found to be less than 50 mg. per 100 cc., the presence of organic hyperinsulinism may be suspected. The shape of the blood sugar curve is not considered characteristic.

The most direct test for hyperinsulinism would, of course, be the determination of the amount of insulin in the serum. Unfortunately, methods for this determination are complicated and time-consuming, and are not yet applicable for routine use. However, even a crudely performed bioassay for serum insulin, as was made in the case which we shall report, or bioassay by injecting an extract of tumor tissue into the peritoneal cavity of a rabbit, as described by Runge, Gilbert, Pelphrey and Gaddy[18] and by other authors,[1] is helpful in confirming the diagnosis.

Case Report

A 40 year old white woman, Gravida III, Para III, was admitted to the hospital on April 15, 1958, because of a tentative diagnosis of hyperinsulinism. Menstruation had

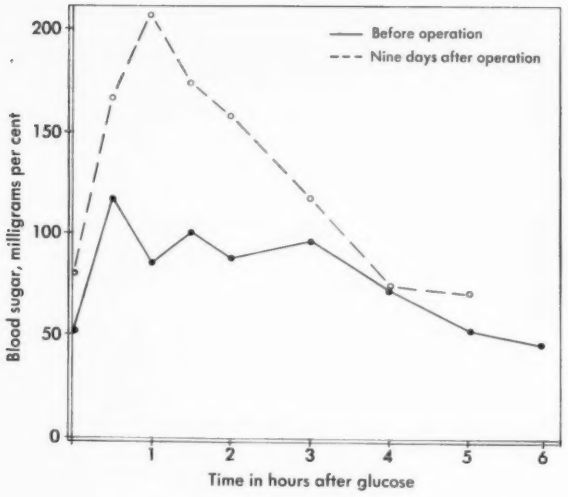


FIGURE 1. Results of glucose tolerance test before and after operation.

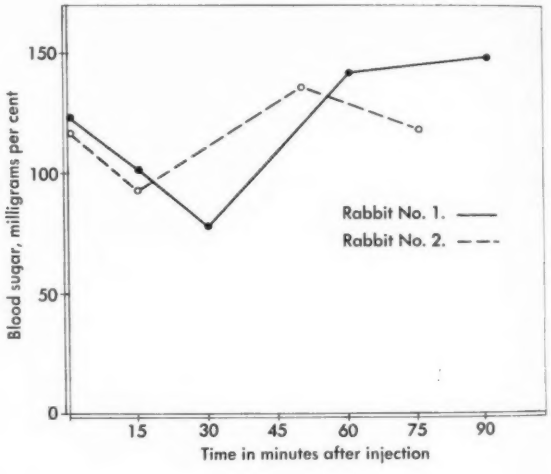


FIGURE 2. Response of the concentration of blood sugar of two fasting rabbits to the intraperitoneal injection of serum obtained from a fasting patient with an islet cell adenoma.

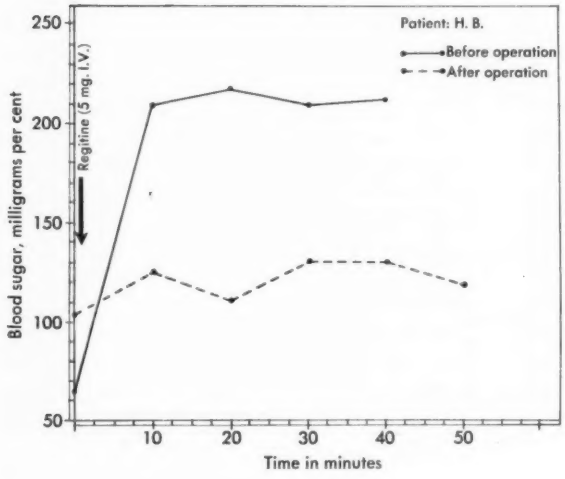


FIGURE 3. Effects of preoperative and postoperative administration of Regitine methanesulfonate on the concentration of blood sugar.

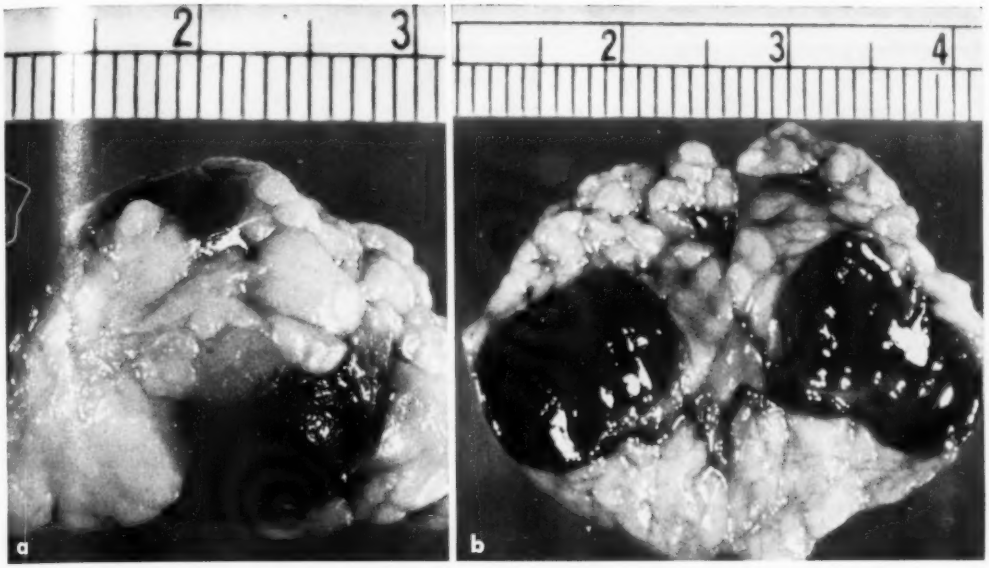


FIGURE 4. Islet cell adenoma; a. gross specimen; b. cut surface.

occurred regularly and had been associated with some pain and premenstrual tension and edema.

Her first attack of unconsciousness had occurred in June 1957. Coma had occurred after she had missed a meal, but she had recovered on the next day. On several occasions thereafter, coma had occurred in the early hours of the morning before she had eaten breakfast, and she had not regained consciousness until some form of sugar had been administered. On each occasion, she had regained consciousness quickly after the administration of the sugar. At the onset, the attacks almost always had been associated with menstruation.

The patient was rather obese. The blood pressure was 130 mm. of mercury systolic and 80 mm. diastolic, and the pulse rate was 84. General physical examination did not reveal any other significant findings. An electroencephalogram was normal.

A glucose tolerance test revealed a flat blood sugar curve and a severe hypoglycemic response (figure 1). After the patient had fasted for 36 hours, the concentration of blood sugar dropped to 39 mg. per 100 cc., and she became disoriented. The administration of fruit juice revived her immediately.

The eosinophil count was normal. When determined on two occasions, the values for the 24 hour excretion of 17-ketosteroids were 17.2 mg. and 12.5 mg., respectively; the values for the excretion of 17-hydroxycorticoids were 10.0 mg. and 8.9 mg., and the values for the excretion of creatinine were 1,553 mg. and 813 mg. The urinary excretion of gonadotropins was normal.

Blood was withdrawn from one of the patient's veins while she was fasting, and 2 cc. of the serum was injected into each of two rabbits that had been fasting for 24 hours. Subsequently, the concentration of sugar in the blood of the rabbits dropped to a level that indicated the presence of insulin (figure 2).

While the patient was fasting, 5 mg. of Regitine methanesulfonate was administered intravenously in order that we might observe its effect on the concentration of the blood sugar. The value for the blood sugar was determined immediately before the drug was administered and every 10 minutes for 40 minutes thereafter. The blood pressure was taken before the drug was administered and every minute for 10 minutes thereafter. After the administration of the drug, the concentration of the blood sugar increased to more

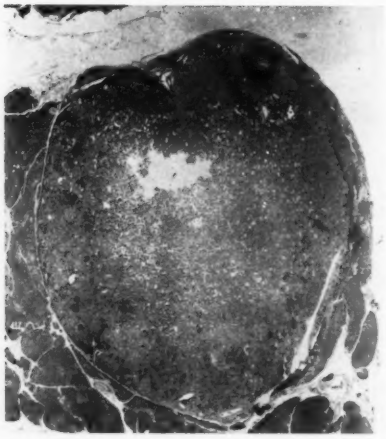


FIGURE 5. Photomicrograph of islet cell adenoma. (Hematoxylin-eosin stain, x 10.)

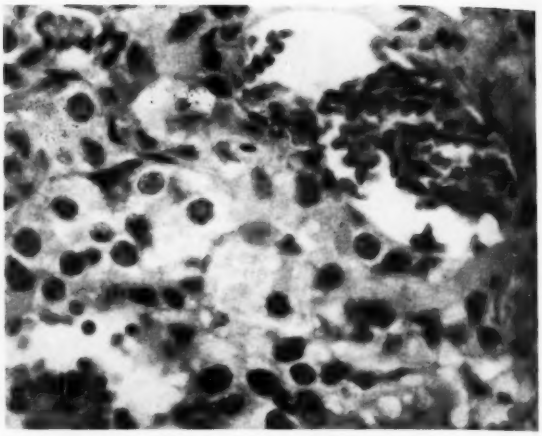
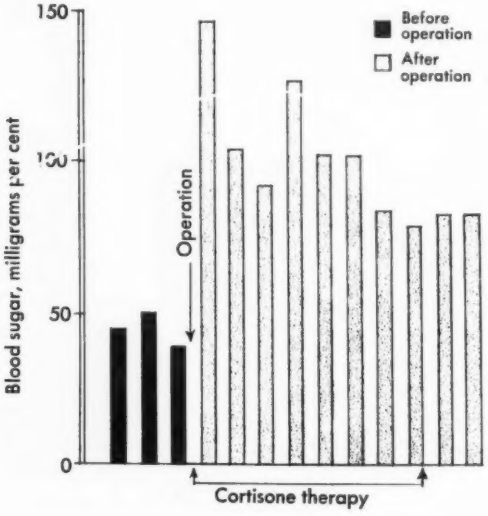


FIGURE 6. Photomicrograph of islet cell adenoma. (Hematoxylin-eosin stain, x 475.)

than 200 mg. per 100 cc. and remained at that level for at least 40 minutes (figure 3). There was no significant change in the blood pressure.

On May 5, 1958, an exploratory operation disclosed a bluish tumor, 2 cm. in diameter, on the lower anterior border of the distal third of the pancreas (figure 4). The excised tumor became dark reddish-purple when exposed to the air. The tumor was an encapsulated islet cell adenoma (figures 5 and 6).

FIGURE 7. Concentration of blood sugar before and after operation.



Cortisone was administered as a precautionary measure before, during and after the operation. Postoperatively, the patient felt a numbness of her face and complained of nausea. Whenever these symptoms were pronounced, the blood pressure was taken and the concentration of the blood sugar was determined. The blood pressure remained within normal limits. The value for the blood sugar was increased during the first few days after the operation, but it subsequently returned to normal (figure 7). Regitine methanesulfonate was administered one month after the operation, but it did not have any significant effect on the concentration of the blood sugar (figure 3).

The patient has been free of attacks since the operation, and the concentration of blood sugar has remained within normal limits.

Comment

The Whipple triad necessary for the diagnosis of hyperinsulinism was present in the case that we have reported. The laboratory findings eliminated the adrenal and pituitary glands as a possible cause of the hypoglycemia. The Regitine test was performed be-

cause of the findings of Runge, Gilbert, Pelphrey and Gaddy,[18] who used this test in a case of hyperinsulinism and coincident hypertension. In their case, the blood pressure decreased after the administration of this drug, but they did not check the concentration of the blood sugar. In our case, there was no significant change in the blood pressure, but the concentration of blood sugar increased to more than 200 mg. per 100 cc. and remained at that level for at least 40 minutes. This effect could not be reproduced after removal of the tumor. The drug did not produce an increase in the concentration of blood sugar when it was administered to a group of normal persons. In one patient with functional hypoglycemia, there was a decrease in the concentration of the blood sugar, but it subsequently returned to normal.

Conclusions

It is too soon to make any definite statement regarding the value of the Regitine test in cases of hypoglycemia or on the possible mechanisms involved. We believe, however, that this test should be performed in cases in which the presence of an islet cell tumor is suspected, since this will enable one to determine the value of the test. The use of a crude bioassay for insulin also may be of some diagnostic value.

We are grateful to Dr. John Owen for the microdeterminations of the concentration of the blood sugar.

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The Solitary Pulmonary Nodule: A Critical Evaluation

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GEORGE J. MAGOVERN AND EDWARD M. KENT*

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In a series of 1,639 cases of solitary pulmonary nodules treated by surgical excision, the incidence of malignancy was 34 per cent. The incidence of malignancy in nodules found in x-ray screening programs has been reported as 3 and 4.5 per cent. Application of the Rhoads formula for preventive cancer surgery vindicates surgical resection of solitary pulmonary nodules when lesions having concentric lamination, total calcification or a large central core of calcium are eliminated.

THE wisdom of treating a solitary pulmonary nodule by surgical excision has been established by multiple reports substantiating the high incidence of malignant neoplasms in these lesions. However, in recent papers a number of authors[1-5] have challenged the validity of previous communications by presenting a low incidence of malignant disease in patients having solitary nodular lesions of the lung. Clarification is necessary, since resectional therapy will effect a cure in approximately 45 per cent of cases of malignant pulmonary nodules, with the salvage rate increasing to as high as 75 per cent if the lesion is asymptomatic.[6-8] While survival is less likely following removal of a metastatic nodule, 30 per cent or more of these patients may be saved by means of surgical treatment.[9]

In 1956 Davis, Peabody and Katz[6] in an admirable review article analyzed a combined series, taken from the literature, of 1,203 cases of solitary pulmonary nodules; the incidence of malignancy in this series was 36.7 per cent.

In contrast, in 1958 Taylor, Rivkin and Salyer[10,11] found the incidence of malignant neoplasms was 9.7 per cent in 236 patients with pulmonary nodules who were treated in a military hospital. Our own experience now includes 296 cases of resected coin lesions, of which 124 have been previously reported,[12] with 39.5 per cent of the total series involving malignant tumors (table 1). In table 2 we have summarized the reported findings in 1,639 surgically excised lesions, of which 550 (34 per cent) were malignant. Although cri-

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teria for surgical treatment have varied, the requirements for inclusion in our current series were as follows:

1. A diameter between 1 and 6 cm.
2. A moderately well-circumscribed spheroid or ovoid nodule.
3. A lesion surrounded by lung.
4. No evidence of major obstruction of the bronchi.
5. No adjacent inflammatory or atelectatic component.
6. No significant hilar, mediastinal, diaphragmatic or pleural involvement.

Case selection certainly influences the percentage of malignant lesions treated by surgical excision. In our own group we have eliminated lesions having concentric lamination, total calcification, or a large central core of calcium. Undoubtedly numerous asymptomatic lesions remain undiagnosed or untreated.

Roentgenographic Screening Programs

While impressive statistics related to surgically excised nodules have been accumulated, Holin and associates[1,2] and Comstock, Vaughan and Montgomery[3] have approached the problem by reviewing films taken in large public health chest x-ray screening programs. The former reported only 3 per cent and the latter only 4.5 per cent of proved malignancy in solitary pulmonary nodules. As emphasized in part by the authors themselves, evaluation of data in their reports indicates the following obvious unavoidable deficiencies in selection and follow-up:

1. The follow-up status of 3.3 per cent of Holin's group of 666 patients was unknown, and information concerning an additional 10.4 per cent was incomplete. Unhappily, experience has shown that when patients actively treated for cancer are followed, many in the "unknown" category are found to have died from their disease.

2. The preponderance of the younger age group also favored the incidence of benignancy in Holin's statistics. When cases of men more than 45 years of age with noncalcified nodules greater than 39 mm. in diameter and not sharply circumscribed were analyzed separately, the rate of malignancy increased to 35 per cent.

3. Since malignant lesions more commonly produce symptoms than do benign nodules, the possibility must be considered that patients with active symptoms sought care and study by physicians rather than responding to an x-ray screening program.

4. The initial films in the survey were of the 70 mm. type. This would seem to favor omission of less well-circumscribed lesions of the malignant class. Indeed when more refined technics were employed in the study, 207 nodules, all nonmalignant, were shown to have

TABLE 1

CLASSIFICATION OF 296 SOLITARY PULMONARY NODULES IN AUTHORS' SERIES (1948 TO 1958)

Benign (histologically proved)	
Granuloma (nonspecific)	140
Tuberculoma*	3
Chronic pneumonitis	5
Bronchial cyst	2
Hamartoma	20
*Histoplasma**	3
Arteriovenous aneurysm	1
Lipid pneumonia	1
Abscess	4
	179
Malignant (histologically proved)	
Primary bronchogenic carcinoma	94
Bronchial adenoma	13
Metastatic malignancy	7
Lymphosarcoma	1
Fibrosarcoma	1
Alveolar cell carcinoma	1
	117

*Includes only those lesions with positive identification of microorganism.

TABLE 2

INCIDENCE OF MALIGNANCY IN SOLITARY PULMONARY NODULES TREATED BY SURGICAL EXCISION

YEAR	AUTHOR	CASES	MALIGNANT		PER CENT MALIGNANT
			Primary	*Metastatic*	
1944	Thornton	23	14	3	74
1948	Effler	24	3	1	17
1948	Obrien	21	9		43
1950	Sharp	55	14	3	31
1950	Husfeldt	24	9	2	46
1951	Abeles	20	7	1	40
1951	Effler	16	6	1	44
1951	Fink	56	18	3	38
1952	Hare	6	2	1	50
1952	Wolpau	24	8	2	42
1952	Bell	23	11	1	52
1952	Condon	27	18		67
1953	Storey	40	4	3	18
1953	Hood	156	38	17	35
1953	Deans	76	17	1	24
1954	May	36	8	4	33
1954	Jones	14	1		7
1954	Meckstroth	70	15	12	39
1954	Wu Shao-Ching	9	1		11
1955	Wilkins	77	29	6	45
1955	Higginson	39	6	1	18
1955	Axtmayer	9	2	1	33
1955	Cohen	11	2		18
1956	French	36	4		11
1956	Davis	215	91	10	47
1958	Taylor	236	21	2	10
1959	Authors' series	296	110	7	40
	TOTALS	1,639	468	82	34

either definite or probable calcification.

5. The natural history of small malignant pulmonary nodules is not fully known, but Rigler[5] has observed tumors of this type which required as long as six years to produce significant symptoms and death. No definite diagnosis was made in 86.2 per cent of the persons in Holin's study. The ultimate fate of these individuals will be of interest.

6. In Comstock's series 88 solitary nodules were detected in 300,000 x-ray examinations. When lesions less than 12 mm. in size and those with notable calcification or lamination are excluded, the malignancy rate rises from 4.5 to 12 to 14 per cent,* despite the predominance of younger persons in his series.

Perhaps the most significant difference between the two methods of study is one of approach. In screening programs, nodules are presumed benign until proved malignant. Surgical treatment for these patients is based on the belief that these lesions should be considered malignant until definitely proved benign.

*The exact figure is obscured by overlapping data.

Military Hospital Reports

The significance of pulmonary nodules seemingly can be estimated more closely by reviewing results noted in military hospitals (table 3). These percentages are influenced by the predominance of young, healthy (favoring benignancy) men (favoring malignancy) in the potential patient group. While Taylor, Rivkin and Salyer,[10,11] in their recent series reported from the Fitzsimmons Army Hospital, eliminated patients having a positive response to Papanicolaou studies, the incidence of malignancy was still 9.7 per cent. Success in finding diagnostic cells in the spu-

TABLE 3

INCIDENCE OF MALIGNANCY IN SOLITARY PULMONARY NODULES TREATED IN MILITARY HOSPITALS

YEAR	AUTHOR	CASES	MALIGNANT		PER CENT MALIGNANT
			Primary	*Metastatic*	
1948	Effler	24	3	1	17
1953	Storey	40	4	3	18
1954	Jones	14	1		7
1958	Taylor*	236	21	2	10
	TOTALS	314	29	6	11

*Series previously reported by Grow (1948), Mahon (1950) and Gregory (1955) were included in Taylor's group with elimination of some malignant nodules due to more exacting criteria for selection.[11]

tum or bronchial washings of patients with malignant nodules has varied from 3 to 53 per cent.[6]

Somewhat stimulated by Holin's work, Taylor, Rivkin and Salyer[10,11] and Mitchell and Taylor[4] have reviewed their own experience in an endeavor to establish criteria for selecting nodules requiring surgical treatment. They feel one's index of suspicion should be tempered by findings of sharp, smooth circumscription, lamination and permanent calcification, or—particularly in areas where coccidioidomycosis and histoplasmosis are endemic—by the results of properly conducted specific skin tests.

Indications for Preventive Surgery

Rhoads,[13] who studied the broad problem of preventive surgery in the field of cancer, has resolved the multiple factors involved into a mathematical formula (table 4) which we feel is worthy of application to the solitary pulmonary nodule. Five factors are considered: (1) percentage of lesions which are or become malignant, (2) percentage of innocent lesions which would not ordinarily require surgery, (3) operative mortality of the procedure as carried out prophylactically, (4) five year survival rate for those operated on prophylactically (before the diagnosis is otherwise established), and (5) five year survival rate for patients who are operated on when the diagnosis is established by other means (table 4).

As with any formula, the data used in calculation determine the result. If we employ conservative estimates, the Rhoads ratio is 4.6:1 for solitary pulmonary nodules (table 5). Since the ratio is greater than 1:1, the wisdom of preventive surgery is vindicated. Application of this formula to specific groups, e.g., young women with sharply circumscribed nodules, may rightfully exclude lesions in certain categories from surgical treatment.

When Holin's figure of 3 per cent malignancy is introduced in the formula, the Rhoads ratio is still greater than 1:1. For the purpose of our calculation several unknown values are involved. In the absence of reliable statistics, 2 per cent seems a conservative estimate of the number of benign lesions presenting as nodular lesions for which surgical treatment will eventually be desirable. Although the rate of cure of malignant nodules followed by serial x-rays may be higher than the 8 per cent indicated in table 5, the weakness of this approach to treatment is emphasized by the frequent ineffectiveness of follow-up attempts plus the variable progression of the disease.

TABLE 4

RHOADS'[13] FORMULA FOR DETERMINING A NECESSARY CONDITION FOR PREVENTIVE SURGERY

M = Operative mortality, per cent
I = Innocent lesions, per cent
C = Cancer incidence, per cent
S-1 = Five year survival rate after preventive surgery
S-2 = Five year survival rate after "therapeutic" surgery
Then MI = loss due to preventive surgery

$$\frac{C\ (S\text{-}1 - S\text{-}2)}{MI} > 1$$ is a necessary condition for preventive surgery

TABLE 5

APPLICATION OF RHOADS' FORMULA TO SOLITARY PULMONARY NODULES

M = 1 per cent*
I = 87 per cent†
C = 11 per cent‡
S-1 = 45 per cent
S-2 = 8 per cent§

$$\frac{11\ (45\text{-}8)}{1 \times 87} = 4.6{:}1$$

*There has been no mortality from exploratory thoracotomy and local resection in our own series. Actually, with competent surgery and anesthesia, mortality figures will probably run less than 0.5 per cent.

†Allows only 2 per cent for benign lesions which would eventually require surgery for abscesses, cysts, granulomas, etc.

‡Average per cent malignancy reported from military hospitals.

§Eight per cent is a common over-all, five year survival figure for bronchogenic carcinoma, since many are inoperable or nonresectable.

Comment

Because of a recent tendency to minimize the malignant potentialities of the solitary pulmonary nodule, we have once again reviewed our experience with these lesions. These data are presented briefly, because our over-all results and conclusions closely parallel those previously reported. Since application of chest x-ray studies in military personnel approaches or surpasses the scope of public health surveys, the average of 11 per cent malignancy in nodules seen in military hospitals indicates that the interpretation of statistics gathered in screening programs has been misleading. Consideration of the deficiencies of the screening program as applied to this problem clarifies to a certain extent the discrepancies which have been noted.

While application of the Rhoads formula for necessary conditions for cancer surgery verifies our feeling that these lesions should be treated surgically, the use of this formula eventually may also help to avoid surgery in selected instances. Further exploration along these lines seems advisable if one is conscious of the pitfalls of applying a mathematical method to clinical decisions.

Summary

1. The over-all incidence of malignancy in surgically removed pulmonary nodules has been 34 per cent.

2. The incidence of malignancy in nodules found in x-ray screening programs has been reported as 3 and 4.5 per cent.

3. The actual incidence of malignancy may be more accurately reflected in reports from military hospitals where 11 per cent of pulmonary nodules are in this category.

4. The deficiencies of the screening program method of analysis are reviewed.

5. Application of the Rhoads formula for preventive cancer surgery vindicates the use of surgical resection of solitary pulmonary nodules when lesions having concentric lamination, total calcification, or a large central core of calcium are eliminated.

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Alcoholism, a Local and National Problem

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The problem of alcoholism encompasses all facets of human life. Factors contributing to problem drinking include social pressures, personality problems, constitutional predisposition and habituation.

In addition to expanding education programs for adults, we can protect our young people from possible future alcoholism by providing education on the effects of alcohol in our public schools. Every state has a law calling for such instruction, but few schools provide it.

Physicians should take an active part in the program to educate the public about alcoholism and attack the stigma and prejudices which still exist. Alcoholism will not be prevented until nondrinkers and nonalcoholics cooperate to help in recognition and treatment.

ROBERT C. RAINIE

ALCOHOLISM ranks as the fourth most prevalent disease in the United States. Authorities estimate that about 700,000 women and 3,900,000 men are now "problem drinkers." Why has this problem assumed such national prominence?

Perhaps we should first look at our drinking customs. There are some 70 million people in this country who drink. Households in which alcoholic beverages in one form or another are not served are certainly difficult to find, and in many homes a substitute for the abstainer is not offered. Even many of our students who have not yet graduated from high school can boast of having had that first drink. It is said that one of the best ways to introduce children to intoxicating beverages is to have them witness drinking in the home. This may be open to controversy.

Recently in New Hampshire representatives of the three major faiths, discussing social drinking, recognized that the reasons for drinking are complex and often hidden from the drinker himself and from society. It is important that church people realize the varied and mixed values which those who drink find in this practice. The reasons include satisfaction of aesthetic tastes, adherence to social and cultural custom, festive celebration on important occasions, a sense of prestige, comfort which comes from conformity to demands of a social group, breaking through social, ethical and moral barriers, as a tranquilizer, and

escape from boredom. But how can one predict which social drinker will find himself one day a problem drinker?

Various sources reveal data on drinking habits in ancient and medieval times and prove that alcoholism has found its way down through the years and is no new problem.[1] In ancient Egypt one day each month was dedicated to drunkenness. In early Rome, when wine was scarce, women and men under 30 were not supposed to drink; but later, when wine became plentiful, everyone drank, and people endeavored to outdrink each other. This custom was eventually outlawed, but other festive occasions continued.

The early exposure of children to alcohol is not unique in the United States. Mangin[2] has found that small Peruvian children are given corn beer, and everyone over the age of 16 drinks in that country. Alcoholism in French school children has become such a problem that restricting laws have been passed.[3] The male Chinese child is introduced to wine casually, but is expected to drink and to know his capacity.[4]

It is unfortunate that our children are not better versed in the use, abuse, side effects and undesirable complications of alcoholic beverages either at home or in school. Although every state in this country has a law which calls for alcohol education in public schools, few schools provide any, let alone adequate, instruction.[5] This is where we can begin to protect our youth from possible future alcoholism. To most teen-agers, drinking is a "smart aleck" stunt and a big joke. The tipsy, talkative, tempting female may be having a wonderful time at a party, relieved of those restricting inhibitions, and yet in a few years she may progress into that confused, lonely, anxious, unpredictable and uncontrollable state of problem drinking. One young socialite started drinking at the age of 15 and claimed she liked the taste of it from the start. She boasted of being "a two-fisted drinker who can drink any man under the table." She loved to be young, healthy, athletic and popular—yet within six years she was addicted to alcohol and barbiturates.

Most of the patients who are admitted to the New Hampshire Division on Alcoholism confess to social drinking in their teens. These young people start drinking because they want to keep up with their companions, don't want to be left out of social activities, and don't want to be ridiculed. This indeed is a strange human fear which eventually sets the stage for a possible future tragedy. In addition, therefore, to our rapidly expanding adult education program, our attention should be focused on a detailed instruction program for the high school student.

The interval between those first innocent drinks as a social function and the stage of problem drinking where intoxication is maintained for sustained periods varies from 5 to 20 years. The true social drinker is distinguished by the fact that the alcohol is secondary to the conversation and the enjoyment of companionship at a social gathering. In other words the use of alcoholic beverages in our society serves a social function, reputedly producing a relaxation of some superficial inhibitions and thus allowing for a warmer, more intimate atmosphere. For most people this type of drinking is satisfactory and can continue for years without serious harm. And yet who can tell which party-goer is going to find an ever-increasing need for that method of relaxation?

The step beyond social drinking finds the victim going to a party primarily for the liquor he knows will be served. This person, if he has keen insight, might well consider himself on the road to becoming a problem drinker. To fortify himself he will have a few drinks before going to the party, and while there he will sneak a few extras to achieve the desired effect. Thus he loses control and drinks to intoxication without intending to, a definite deviation from accepted social practice. Since there is no absolute cure for alcoholism, it is at this stage that intervention can do so much to alter the progressive deterioration of chronic drunkenness. Unfortunately the disgrace which has long been associated with this disease has caused the victim to conceal his illness for some time before enlisting professional aid.

Among various factors which contribute to

the gradual metamorphosis from social to problem drinking are social pressures, personality problems, desire to escape, constitutional predisposition, habituation, and economic, religious and family crises.[6]

Apparently there can be a cellular craving for alcohol. In a minority of alcoholics who have trouble with alcohol from the beginning of their drinking history, there is usually a family history of alcoholism that suggests some hereditary predisposition. Those who are insecure in their relations with other people may substitute dependence on chemicals for dependence on others, thus leading to repetitive heavy drinking, a true craving.[7] Other drinkers are characterized by emotional blunting, a tendency to vagrancy, pessimism of outlook, and depression. Ultimately these people lose their ability to work, and become separated from society and completely isolated. The various etiologic factors involved in alcoholism are recognized by the New Hampshire Division, which classifies patients as (1) symptomatic, (2) essential and (3) secondary alcoholics, and also separates the four phases of addiction: pre-alcoholic, prodromal, crucial and chronic.

In Ireland, alcoholism is not yet recognized as a national social problem, although the average Irishman regards all excessive drinking as something inevitable in his country and is suspicious of any movement toward curtailing his right to drink. The prevalent belief that "a man is no man who cannot drink" makes the problem drinkers reluctant to seek help, although Alcoholics Anonymous has helped to lessen the stigma that is attached to alcoholism.[8]

The 400,000 Indians in New Mexico are presenting a grievous problem with excessive drinking. This is apparently due to underlying psychologic, social, cultural and economic disturbances of the Indian people at this time, when they are undergoing a period of unusual change, stress, dislocation, instability and insecurity. Most of the Indians are poor, frustrated, hungry, discouraged and mistreated. Juvenile drinking is on the increase, and children are left by drunken parents to shift for themselves or are encouraged to share when the bottle is passed around. The New Mexico Association on Indian Affairs believes consumption of alcohol among the tribes will not decline until there is an educational program presenting the facts and attributes of alcohol, beginning in the elementary grades.

Here, then, is our greatest unsolved public health problem—unsolved because it has not been adequately faced or scientifically studied. Although facts about alcoholism have been publicized through magazines, newspapers, radio and television, prevention of this illness will not occur until the 65 million drinkers who are not alcoholics and the 40 million adults who do not drink cooperate to help recognize and treat the early alcoholic.

Of the 4,600,000 alcoholics in the United States it is estimated that in New Hampshire there are 17,500 victims of alcoholic addiction. This unfortunate group excludes no one. At the time of first contact in the New Hampshire Division on Alcoholism over two-thirds of the patients were in the skilled, white-collar, managerial and professional categories. This figure is similar to that reported by Falkey and Schneyer,[9] who studied 316 male alcoholics and found that approximately 8 per cent were professional, technical or managerial personnel, 10 per cent represented other white-collar occupations, some 44 per cent might be called skilled or semiskilled workers, and the remaining 38 per cent were service workers or laborers. In New Hampshire approximately 30 per cent of these people had at least one alcoholic parent and one or more alcoholic siblings, and 20 per cent were married to an alcoholic. Over half were married and living with the spouse when aid was first sought. Falkey and Schneyer pointed out that alcoholics who were married and living with their spouses demonstrated a higher level of social and perhaps psychologic stability than unmarried alcoholics, indicating their ability to adjust to other life conditions with far greater success than those who remained single or whose marriages were broken. This matrimonial durability in the face of years of irresponsible excess drinking may sometimes reflect psychopathology in the spouse of the alcoholic, as suggested by Whalen.[10]

Statistics in New Hampshire reveal that two-thirds of the inmates of our houses of correction and about one-half of our state prison inmates are alcoholics. In one of our larger cities it was recently found that almost half of all children in the "Aid to Dependent Children" category had one or two alcoholic parents. This is quite significant, since no single factor is more important in the development of a child than the specific and continued attitudes manifested toward him by his parents.

Accident data from the National Safety Council show clearly that neither the "drinking driver" nor the driver "under the influence of alcohol" is the major cause of traffic accidents, fatal or otherwise, but it would appear that each year finds this category playing a more conspicuous part. This may not be entirely due to true alcoholism, but it certainly is the misuse, through ignorance, of alcohol by social drinkers. From tests carried out in several large cities it would seem that about 12 per cent of all car operators at any time are driving after having consumed two or more drinks. These surveys also indicated that a minimum of 40 per cent of traffic deaths on our national highways have an alcohol "flavor." A recent study by the New York City Police Department uncovered the somber evidence that 55 per cent of motor vehicle operators who were killed at the wheel or who died soon after an accident had alcohol concentrations of from 0.10 to 0.40 per cent in their systems at the time of the accident. The solution to the drinking-and-driving problem lies in constructive future publicity and education.

It has become increasingly apparent that the revenue realized from the beer and liquor business is hardly adequate to offset the cost of support of our alcoholic population. In 1955 California made about $39 million from its liquor taxes while the state's estimated expense was between $120 million and $300 million. One county in North Carolina is suffering a total cost resulting from alcoholism and drunkenness in excess of $50 million, while the revenue for the whole state is only $21 million. New Hampshire in 1956 made nearly $6 million from its alcoholic beverage business, which is woefully inadequate to cover the cost of prison and jail care, hospitalization, absenteeism in industry, accidents, rehabilitation, and dependent care resulting from alcoholism.

Wage losses through absenteeism in industry due to excessive drinking are computed at $432 million per year. In addition the loss of valuable personnel, who fall victim to alcoholism after years of investment in their training, is costing industry an astronomical amount each year. On the other hand, one must remember that the liquor industries employ a great many people, are important purchasers of goods and services from many other industries, provide millions of dollars each year to charitable, educational and other nonprofit organizations, and have assumed a position of considerable significance in our national economic pattern.

Here, then, is a tremendous local and national problem encompassing all facets of human life—social, familial, criminal, educational, industrial, economic and psychologic. It is hardly possible to change the drinking habits of a population, but it is possible, through education, to bring about the early recognition of alcoholism and to institute prompt therapy. Many groups are cooperating to determine the eventual solution to this disorder.

Active Organizations and Their Programs

In September 1939 a group of six recovered alcoholics in Akron, Ohio, formed a self-help organization which has now grown to 6000 members in the Chicago area alone. Among the numerous resources available in the treatment of alcoholism, this voluntary fellowship of Alcoholics Anonymous has apparently achieved a success as great as, if not greater than, the efforts of medicine, psychiatry and psychology. It has merely appealed to the problem drinkers to join with others of their kind in mutual support against the uncontrollable need to drink. However, in spite of favorable publicity and widespread recognition, one factor in this "group therapy" has been overlooked, namely, that there are many alcoholics who have the opportunity to join

but for some reason do not, and who therefore obtain little help from this contact. According to Trice,[11] the alcoholic's association with AA depends a great deal on his ability to share basic emotional reactions with others, his loneliness as a result of desertion by his drinking friends, and his belief in the sincerity of the group members. It is through this organization that the New Hampshire Division on Alcoholism receives 20 per cent of its referrals, and following treatment a large number return to an active role in Alcoholics Anonymous.

In 1944 the National Council on Alcoholism was founded with three concepts: (1) Alcoholism is a disease. (2) The alcoholic can be helped and is worth helping. (3) This is a public health problem and therefore a public responsibility. Its goals are prevention through education, rehabilitation and community services. This council does not operate information centers or clinics, nor is it immediately responsible for rehabilitation of any person. These are the responsibilities of its community branches, the local committees. The National Council is extremely active in community organization and community action, with one of the spearheads of its attack being the family service agency. Consultations are held with legislative, industrial, medical, hospital and educational leaders in an attempt to change the stigma of public opinion and get acceptance of the medical fact that alcoholism is a disease. This must be accomplished without taking a position either for or against the use of alcohol, because this committee is neither wet nor dry. It sponsors scientific meetings, helps create new local committees, and acts as counselor for programs, treatment technics, research projects and public education devices. This council provides the community, and the professions, industries and agencies involved, with the medical, scientific and practical knowledge needed to rehabilitate alcoholics and prevent alcoholism.

Throughout the country, treatment centers for alcoholism have been developed. The first city-operated outpatient alcoholic clinic in the country was the Adult Guidance Center established in 1951 in San Francisco, which has an alcoholism rate twice that of Boston and four times the national average. Center physicians stress the family doctor's potential role in treating alcoholism. In their opinion the sheer size of the problem is evidence that institutions cannot handle it entirely. The cooperative, understanding general practitioner is able to achieve excellent results by helping the alcoholic rebuild self-confidence and by establishing rapport with other members of his family. This center stresses the social-medical management of alcoholism through the cooperative ventures of six physicians, nine psychiatric social workers, two psychologists and four nurses. It is only one of many centers.

Most of the clinics for alcoholism throughout the country follow a similar pattern of study, investigation and management. Success with the problem drinker depends on accepting him as a person with a legitimate illness who is seeking help voluntarily, who recognizes that he has a drinking problem, and who honestly wants to do something about it. These patients have been greatly encouraged by the optimistic attitudes of the physician and psychiatrist, rather than the former hopeless reaction that "all is lost" if the patient takes a drink. Understanding the problem of alcoholism and approaching the addict in a noncritical, enthusiastic atmosphere help to create mutual trust and insight. The intent of most clinics is not just to "dry out" the patient but rather, through medical, sociologic and psychiatric evaluations, to rehabilitate him to being a useful citizen. This is accomplished through individual and group psychotherapy, education of the patient about his illness, counseling of the alcoholic's family, and frequent and regular outpatient interviews. In Concord, it is recognized that those patients who use the facilities of the unit for social contact and recreation during their free time have much better records of sobriety than do those who lose contact soon after discharge. Patients are encouraged to visit the unit as frequently as possible after discharge, since their contacts there remind them that they are alcoholics and that they cannot take that first drink.

The New Hampshire Division on Alcoholism sends out frequent bulletins to all doctors in

the state and to other interested organizations. Unfortunately the busy practicing physician finds it too easy to refer these pamphlets directly to the wastebasket, which explains why so many physicians in the state are unaware of the existence of such a unit or program for alcoholics.

The universal goal of all clinics is to reach as many alcoholics as possible, particularly the early victims and the hidden addicts. They must be made to realize that the sense of guilt and shame which is the companion of alcoholism has now begun to dissolve because of the concrete interest and financial support given by outstanding people. Today the alcoholic is assured that individuals, whether they are addicts or not, have seen fit to help him in his personal battle to escape this tremendous burden. One of the bulletins distributed by the New Hampshire Division was an excellent "Letter to the wife of an alcoholic" which was prepared because of many inquiries from these wives. It explains the nature of the illness, the function and program of the Division, and how the wife and the Alcohol Unit can cooperate in rehabilitating her husband. Emphasis is laid on the facts that progress is constantly being made and that it is far from a hopeless problem. A recent survey made by the California State Alcoholic Rehabilitation Commission demonstrated that 50 per cent of patients two years out of center treatment had stopped drinking, another 20 per cent were improved, and the remaining 30 per cent had not been helped.

Those who have read "The Twelfth Step" by Thomas Randall[12] will recognize the complicated problems these alcoholics have. This book was written by an intelligent, educated alcoholic who has now enjoyed a long period of sobriety following a brief course of therapy at the New Hampshire Division. This book may be recommended highly to improve the understanding and management of the alcoholic by the family doctor, who can become better acquainted with the addict's mental processes, secret yearnings, philosophies of life, and hidden ambitions and thus help prevent and correct this complex disorder.

As soon as the patient can realize and accept the fact that he is and always will be an alcoholic, his outlook for sobriety is much more favorable. There is no such thing as an ex-alcoholic. Sobriety will be maintained only as long as the addict insists on coffee or tomato juice in place of that first drink which is offered by so many friends. One difficult obstacle is the overconfidence which develops in the patient who has been sober for several months with ANTABUSE® or psychotherapy. He feels certain he can control just one drink, but before long finds himself once again on a "lost week end." A woman recently admitted to the Alcohol Unit was an elegantly groomed, sophisticated, educated mother of two grown children who always had taken a cocktail or two before dinner without trouble but for the past year had found herself drinking constantly for several days during periods of depression, loneliness and nervousness. On the verge of becoming an uncontrolled problem drinker, she fortunately had the intelligence and insight to recognize her difficulty and seek help.

At the present time in New Hampshire, the North Conway Foundation and the Belknap County Committee on Alcoholism are the only organizations assisting the Concord Division and its 10 bed unit in the understanding and treatment and education of alcoholism. According to Director Camille Lambert,[13] it is anticipated that the Concord Unit will be decentralized and six outpatient clinics will be established throughout the state which will provide a closer contact with alcoholics and be much more effective in reaching the hidden alcoholic. For those patients whose condition is poor, hospitalization will be provided by general hospitals. It is hoped to create and expand community committees on alcoholism which would be affiliated with the National Council on Alcoholism. We, as physicians, should take an active part in this program to educate the public about this disorder and attack the stigma and prejudices which still exist. The New Hampshire Division on Alcoholism is eager to help any group interested in alcoholism and the rehabilitation of the alcoholic. It is anxious to cooperate in any manner possible to assist the alcoholic in achiev-

ing the goals of his prayer: "God grant me the serenity to accept the things I cannot change, the courage to change the things I can, and the wisdom to know the difference."

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Postgraduate Clinical NOTES

126. SIGMOIDOSCOPIC EXAMINATION

The value of sigmoidoscopic examination increases as experience is gained. Routine examination of the asymptomatic patient may be unproductive because the endoscopist is not looking for anything; thus, a short and pertinent history is necessary to put the examiner on guard. Careful digital examination may locate a lesion on the posterior wall of the ampulla just inside the sphincters which the sigmoidoscope may not visualize, or a telltale mass may be palpable in the rectovesical pouch or cul de sac. Nothing is more stimulating to the examiner than to find blood in the ampulla or the lower part of the sigmoid colon. Thus, there should be no preparation of the symptomatic patient with enemas. We have found repeated sigmoidoscopic examination of the symptomatic patient to be of great value. A small lesion missed at the time of the first examination may be visualized subsequently. The finding of blood coming down from above impels the examiner to order repeated roentgenograms made with special technics to locate a lesion not seen in previous roentgenograms. The use of Papanicolaou smears for cancer located above the rectum, or in the blind area of the sigmoid colon just above, is of inestimable value. Finally, the patient who cannot tolerate proctoscopic examination because of pain may be examined under the influence of anesthesia, provided the symptoms warrant it.

Rupert B. Turnbull, The value of sigmoidoscopic examination, *Diseases of the Colon and Rectum*, January-February 1959, pp. 33-35

Nutrition and Athletic Performance

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Diet and Athletic Performance

In subsequent articles in this series, attention will be given to the general significance of diet faddism to the practicing physician. Suffice it to say that diet fads are dangerous to the patient on at least three grounds: (1) Nutritional—by relying on the supposedly unique qualities of near-magic foods (e.g., blackstrap molasses, kelp, etc.), the patient often places himself on a highly unbalanced ration conducive to deficiencies. (2) Financial—the cost of health foods, special preparations, etc., is so high that it drains away resources needed for medical or dental care, education of children, etc. (3) Intellectual—by casting aspersions on "organized" medicine and "official" nutrition, the practice of diet faddism makes the patient less receptive to sound medical and hygienic advice and more prone to fall prey to even more dangerous forms of quackery.

The purpose of this discussion is not, however, to deal with the more widespread food fads, but to examine one special aspect frequently attached to competitive sports. From conversation and correspondence with a number of coaches, deans of colleges of physical education, athletic directors and team physicians, we have become convinced that the athletic variety of diet faddism is extremely widespread. In a single university, each coach may, through the agency of various training talks and team instruction, put his boys on his own idea of a "winning" diet. It may entail prolonged daily periods of avoiding fluids, omitting whole classes of wholesome foods, ingesting large amounts of unnecessary, expensive items (royal jelly was used in a well-known college), or slanting the diet toward a ration excessively high in saturated fats.

Such odd practices may not have experimental foundation, but they do have historical precedents. For example, one of the most popular training-table practices has been the consumption of large quantities of meat, supposedly destined to replace the protein "losses" incurred during severe muscular work. This practice has been traced back to the fifth century B.C. Until that period, the diet of the Greek athletes had been mainly vegetarian, consisting of porridge, meal cakes, figs, some

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fresh cheese, and meat eaten only occasionally as relish. The change took place shortly after the Persian Wars, when a trainer, Dromeus of Stymphalus (who twice won the long race at Olympia, in 456 and 460) introduced the meat diet. This new diet (the appearance of which also coincided with the rise of professionalism in Greek sports) was meant mostly for wrestlers. Classification by weight was unknown and the heavyweight had a decided advantage. Such extremes in athletic training were denounced by Hippocrates as producing "a dangerous and unstable condition of body."[1]

Many of the more bizarre nutritional beliefs of coaches echo Greek, Roman or even older tribal advice. For example, a current best seller[2] attributes to honey a number of exceptional properties for "athletic nutrition." While eating honey is a pleasant way to take carbohydrates, there is no evidence presented in this book or elsewhere showing honey to be inherently superior to other carbohydrate foods from a physiologic viewpoint. Because the general practitioner in his frequent work as a school physician and hence as team physician, as well as in his private doctor-patient relationship, may have to pass judgment on some of the dietary practices of athletic departments, a review of what we *do* know of the effect of diet on athletic performance may be found useful.

Timing and Relative Size of Meals

The influence of the spacing, number and relative size of meals has been studied experimentally in relation to *prolonged* physical work. Haggard and Greenberg, using a bicycle ergometer, showed that frequent meals improved over-all performance. They concluded that a pattern of five meals a day led to a total work output greater than that obtained with three meals. Further reduction to two meals a day (by omitting breakfast) led to inferior performance, particularly during the morning. Haldi and Wynn[3] could not duplicate these results under actual working conditions. For example, they did not find a significant increase in the productivity of seamstresses given snacks or meals of various compositions and sizes at midmorning and midafternoon breaks.

Hutchinson[4] concluded that replacing a few large meals with more frequent moderate-sized snacks may lead to higher efficiency through psychologic effects. More frequent breaks in a routine are known to augment production. Hutchinson believes that "with breakfast as a possible exception, the ingestion of food is not followed by any great increase in industrial productivity or by improvement in athletic performance."

Tuttle and co-workers[5] studied exhaustively the effect of omission and variation of composition of breakfast. Omission of breakfast (or its reduction to a cup of black coffee) caused a decrease in the maximal work output (measured on a bicycle ergometer) and increases in reaction time and muscle tremor. Orent-Keiles and Hallman[6] observed that work following no breakfast or an insufficient breakfast precipitated the onset of dizziness and nausea in nonworking subjects.

Causeret[7] related an interesting "natural" experiment performed in South Africa. During the Ramadan period, Moslems there, as elsewhere in the Mohammedan world, eat only two meals a day, one early in the morning and the other at 6 P.M. During the rest of the year, they eat three meals a day. Better performances in timed races were achieved during the period when three meals were eaten than during the Ramadan.

It thus appears that data are not numerous and conclusions are in part contradictory. No detailed, controlled study conducted under actual athletic conditions seems available. Prolonged adaptation to an altered meal pattern could be successful. All in all, evidence at hand does suggest, however, that athletes should have at least three meals a day or perhaps more frequent, lighter meals. The latter pattern may be particularly valuable if the sport practiced is one requiring long hours of effort (e.g., skiing, distance running, swimming, etc.). Exercises of shorter duration should not require a drastic modification of the usual pattern of meal distribution. From the viewpoint of digestion, it makes sense that the last meal preceding an athletic contest should be eaten three hours or so prior to the event. This eliminates the drain on the circulatory system coin-

cidental with active absorption. Conversely, emotions or nervousness felt by the performer prior to entering the contest is less likely to interfere with digestive processes if this last meal is eaten well in advance. (The care and speed with which a small sugar supplement is digested exempts it from such restrictions.)

Meal Composition and Athletic Performance

Carbohydrate and fat—Carbohydrate is known to be oxidized preferentially for muscular work. It has been established that while carbohydrate yields only half as many calories per gram as does fat, the burning of carbohydrate yields more calories *per liter of oxygen* than does the burning of fat. On theoretical grounds at any rate, one might expect that in any sport in which the oxygen supply to the tissues is a limiting factor, using carbohydrate as the chief fuel might prove to be advantageous.

In practice, two main types of studies have been conducted to test the possible advantage of this or that type of distribution of physiologic fuels: (1) those in which subjects exercise following the ingestion of single meals of the desired composition and (2) those in which the subjects are fed for several days a special diet high in a given component (carbohydrate, fat, protein) and low in the others to "saturate" the body with one type of food prior to performance in the postabsorptive state (even after several hours under basal conditions).

Among studies of the first type is that of Haggard and Greenberg, who found that a high carbohydrate meal increased efficiency by 25 per cent. Other investigators have not observed differences of this magnitude. Haldi and Wynn[3] did not find that a high carbohydrate diet yielded superior performance as compared with isocaloric, low carbohydrate meals for swimmers in 100 yd. sprints. They concluded that for exercises of short duration readily available stores were sufficient so that muscular efficiency was not affected by the size or type of pre-exercise meals. Similarly, while Wrightington[8] observed the expected differences in respiratory quotients following ingestion of supplements of glucose or sucrose, there were no significant changes in muscular efficiency.

While the beneficial effect of sugar ingestion for short-term exercise must be considered unproved, there appears to be better evidence in favor of a high carbohydrate diet for prolonged exercise. Marsh and Murlin found the average net efficiency of work (light exercise) to be similar on a high carbohydrate diet, on a normal diet, and on a high fat diet; however, there was a decline in efficiency on the high fat diet following the fourth day. Christensen and Hansen found that a subject could continue strenuous work three times as long on a high carbohydrate diet as on a high fat diet. Christensen also maintained athletes for several days prior to exercise on extremely high fat diets, on high carbohydrate diets, and on mixed diets. He then had the athletes exercise in the postabsorptive state and again found endurance impaired on the high fat diet; it was greatest on the high carbohydrate diet. From determination of respiratory quotients, Christensen concluded that while trained athletes can utilize indifferently carbohydrate and fat during rest and light work, they increase the percentage of carbohydrate used when performing heavy work, if such carbohydrate is available.

Krogh and Lindhard compared in similar experiments efficiency on high carbohydrate and high fat diets and found the muscular efficiency 11 per cent higher on the high carbohydrate diet. Bierring found that the net efficiency was 8.3 per cent higher. Gemmill[9] criticized the latter result as an inaccurate extrapolation. His own recalculation of Bierring's data would yield a 4.5 per cent difference between the high fat and the high carbohydrate diet. Such a difference would still be highly significant in competitive athletics.

When it is recalled that the average American diet contains approximately 40 per cent fat, and usually more when the caloric intake is greater than normal (which it is on athletic diets), and when it is further remembered that the usual practice at training tables is to load athletes with high fat foods (meat, eggs, milk), there are serious questions as to whether,

quite apart from the possible dangers of atherogenesis, the current diets for athletes are even optimal for the coaches' purposes.

Protein intake—One of the most persistent misconceptions in nutrition is Liebig's theory that protein is the primary source of muscular energy. Voit and Pettenkofer in their memorable article in 1866 clearly refuted this theory. Many authors have since supported them in this refutation. Yet the claim that those doing heavy work (miners, construction workers) require more protein than do sedentary persons or even children was repeatedly advanced by unions in wartime. Even the British government had to compromise in its rationing scheme with this idea, which its scientific advisers unanimously denounced as erroneous. Present-day coaches in the United States and elsewhere still agree with the fifth century B.C. Greeks and Liebig in spite of nearly 100 years of experimental evidence to the contrary.

In experiments relating the level of protein intake to work performance, Chittenden claimed that low protein intakes (50 to 60 gm.), on which subjects in training were maintained over a period of five months, actually improved efficiency and well-being to levels superior to the pre-experimental period, in which protein intake had been in excess of 100 gm. However, the experimental controls necessary to demonstrate that the gradual improvement in strength observed by Chittenden was due to reduced protein intake and not to training were absent. At any rate, the experiments did seem to prove that a reduced protein intake did not impair physical performance in any way.

For two months, Darling and co-workers[10] studied three groups, one on a restricted protein intake (50 to 55 gm.), one on a normal diet, and one on a daily protein intake of 160 gm. The subjects engaged in hard manual labor. While neither the low nor the high protein intake appeared to be harmful, neither appeared to be beneficial in regard to work efficiency.

While the *performance* of heavy physical labor or athletic exercise does not increase protein requirements, the *increase in muscle mass* associated with training and conditioning does, like all growth processes, require an adequate supply of good-quality protein. For example, Yamaji[11] noted positive nitrogen balance in subjects who formerly were sedentary and who were submitted to arduous physical training. The nitrogen retention was greater on a diet providing 2 gm. of protein per kilogram of body weight daily than on a diet providing 1 to 1.5 gm. Yamaji noted significant drops in blood hemoglobin and albumin during the beginning of the training period. These he interpreted as indicating that muscle was formed in part at the expense of blood protein. The extent and the duration of the decrease in hemoglobin and even in albumin levels were less on the high protein diet. It must be emphasized, however, that the decreases in blood protein were transient and self-correcting and again were characteristic of transition between sedentary and active periods, not of the athletic period per se.

Water-soluble vitamins—Impairment or elimination of work performance in frank vitamin deficiencies is well known. As readers of POSTGRADUATE MEDICINE know, it is often more difficult to recognize borderline deficiency states. In such cases, what may appear to be a favorable effect of vitamin "supplementation" on performance actually may be the therapeutic effect of the vitamin on a hitherto unrecognized borderline deficiency.

A number of workers have attempted to see whether the ingestion of vitamins *in excess* of the accepted standards might in some way be helpful in meeting the additional stress imposed by exercise. In particular, Simonson and associates[12] examined the influence of a surplus of B complex vitamins on the performance of 12 healthy subjects engaged in five different types of muscular work. No beneficial effects were observed on total output or efficiency, although it was noted that in eight of the 12 subjects flicker-fusion frequency increased, a finding often taken to indicate decreased central nervous system fatigue. Keys and Henschel[13] carried out an extensive series of tests on a group of pretrained army men receiving adequate diets, supplemented by a surplus of five B complex vitamins and ascorbic acid. There were no beneficial effects

noted on endurance, resistance to fatigue, recovery from exertion, or muscular strength and dexterity. Studies conducted in the same laboratory on four healthy young men maintained on adequate diets plus vitamin B_1 administered at five levels ranging from 0.23 mg. per 1000 calories to 0.96 mg. per 1000 calories, indicated no beneficial or detrimental effects on performance in muscular, cardiovascular, psychomotor and metabolic functions. These studies included four series of experiments, each lasting 10 to 12 weeks. Vytchikova[14] suggested that the vitamin B_1 content in athletes' rations should be increased above the usual level of 1.5 to 2.0 mg. per day on the basis of findings that following vigorous exercise both the thiamine and pyruvic acid content of blood are increased. Supplementation of the diet with 10 to 20 mg. of vitamin B_1 per day reduced the level of pyruvic acid in blood to the values found in manual workers engaged in moderate exercise, and it improved reaction time before and after training.

Montoye and co-workers[15] concluded that experimental evidence does not justify recommending additional vitamin B_{12} to athletes. In their experiments, vitamin B_{12} supplements had no beneficial effect on strength and pulse rate recovery after work on a bicycle ergometer. These investigators also were unable to observe positive effects of supplementation in boys living in an institution and tested on running and in Harvard step test performance. The postulate of Bourne[16] based on his review of the literature was to the effect that there must be an increased demand for the B complex vitamins during exercise because of their important role in so many of the biochemical reactions which make energy available for muscular work. This theory would appear a priori to be justified only if the vitamin B content of the diet did not increase in proportion to the additional calories required by exercise and consumed by the subject.

These writers at any rate conclude that there is no evidence that athletic performance is improved by supplementing a nutritionally adequate diet with B complex vitamins or vitamin C. It goes without saying that should the bulk of additional calories required for exercise be provided by such "purified" food stuffs as overmilled rice or refined sugar, additional B complex vitamins might be helpful.

Vitamin E and corn oil—Some of the more radical claims for the beneficial effect of vitamin preparations on athletic performance concern vitamin E. Cureton,[17] while recognizing that the effect of training is paramount during the first 8 to 10 weeks of a physical training program, claims that dietary supplements of vitamin E and wheat germ oil make possible even higher endurance work performances (bicycle riding and treadmill running) and raise such performances above the plateau obtained after 8 to 10 weeks of training. Cureton further stated that such effects appear only in relatively strenuous training programs. In one group of older adults (26 to 65 years) who failed to make good adjustments to a short period of physical training (four to six weeks), the evidence was inconsistent and unstable. The fitness test performance of control subjects living normally was not raised by vitamin E or wheat germ oil supplements. In two matched groups of eight middle-aged subjects each, a dietary supplement of wheat germ oil was effective only in the group which took the physical training parallel with the feeding. While the control group showed little or no change, the experimental groups on wheat germ oil improved more than did the matched group (placed on placebos) in treadmill-running time; brachial pulse wave; auditory, visual and combined vertical jump reaction time; the Schneider index, and the T wave of the electrocardiogram.[17]

The results achieved by Thomas[18] are in flat contradiction to those of Cureton in regard to the influence of vitamin E on athletes in training. Thomas experimented with 30 young male students. Fifteen were given 450 I. U. of alpha-tocopherol acetate daily for five weeks and then were given placebos for five weeks. The other group received placebos first, followed by vitamin E. At the beginning of the experiment and at five and 10 weeks, measurements made of the reclining pulse rate, resting respiratory rate, speed sit-ups, vertical jump, and pulse and respiratory rates immediately after activity showed no differences between

the groups during either test period. In addition, no changes were seen in temperament, in disposition, or in general feeling of well-being. It would appear that a clear demonstration of the beneficial effects of vitamin E has yet to be provided.

Gelatin, glycine and creatine—It has been hypothesized by a number of authors that a diet supplemented with glycine (a precursor of creatine) might increase the concentration of creatine and thereby the potential supply of high-energy phosphocreatine in muscles. Because of its high content of glycine (approximately 25 per cent), gelatin has been advocated as a useful supplement.

Maison tested the effect of glycine and gelatin on endurance (finger extension) and could find no beneficial effect for either substance. Horvath and associates found that glycine supplements neither increased muscle strength nor accelerated the effect of training in hand dynamometer tests. Administration of gelatin did not unequivocally alter creatinine excretion. Robinson and Harmon studied the effects of gelatin on exhausting muscular work on the treadmill and in track exercises and reported that gelatin did not affect the oxygen debt. On the basis of their review of work done on this subject, King and co-workers[19] concluded, "Claims made for especial value of aminoacetic acid or gelatin in the treatment of fatigue or increased endurance are unfounded on theoretical grounds . . . protein of the ordinary diet is fully capable of supplying the aminoacetic acid required by man."

Electrolytes and acid-base balance—The idea that alkalizing agents might alleviate fatigue or shorten the recovery period following strenuous exercise by neutralizing lactic acid has been advanced by some popular writers and often is cited by coaches. Johnson and Black[20] found no significant difference between the effects of glucose and various alkalizing supplements on timed performance during a season of competitive cross-country running. Embden's claim that phosphate preparations increased work output has been attributed by later workers to purely psychologic effects.

There is no evidence that exercise causes a need for salt in excess of the losses accompanying sweating. The problem of salt for athletes is therefore not different from that of workers exposed to hot climates. Salt is indicated only during a period (e.g., one week) of adapting to sudden heat or when the heat is extreme. Additional salt in the food is often better tolerated than are salt tablets.

Alcohol and caffeine—One of today's best-known athletes, the "four minute" miler Chris Chataway, is said to consume fairly copious amounts of beer as part of his training diet. Moderate amounts of wine were consumed by Greek athletes in training for the Olympic games. On the other hand, the majority of coaches frown on the consumption of even small amounts of alcoholic beverages. The rationale for this taboo is that small quantities of alcohol affect the finer coordination movements and larger amounts affect gross coordination.

Studies on the effect of coffee and tea on performance have yielded divergent results, which may be due to differences in reactivity to caffeine. Stimulants such as pure caffeine may tax a person beyond the safe limits of physical capacity. Thus, while they may mitigate fatigue for a while, stimulants constitute a long-range health hazard.

There appears to be no particular reason either to advocate alcohol or mild stimulants such as tea and coffee or to erect a complete taboo against them. The long-term psychologic effects of such taboos may be undesirable. There is increasing feeling among psychologists that, frequently, chronic alcoholics are persons in whom precisely this type of absolute taboo had been instilled concerning the intake of even small amounts of beverages which have low alcoholic content such as wine or beer.

"Crash" Diets

In sports such as boxing and wrestling, present-day athletes, professional and amateur (the latter group frequently including high school students), often place themselves on crash diets combined with dehydration to "make" lower weight classifications. This is a practice to be strongly discouraged. The intention of these athletes is not to attain their most desirable weight from the viewpoint of

health and fitness but rather to compete with an unfair advantage against an opponent who really does belong in a lower weight bracket. In a sense, this is the wheel gone full circle since the meat diet of Dromeus in times when weight classification did not exist. The weight standards have been set up to provide competition on an equitable basis. Violating them by using tricks such as sudden, self-inflicted starvation and temporary dehydration serves no more the ethics of sportsmanship than it does the health of the person involved. The practice has become so widespread that it has received increasing medical attention and has been the object of editorial condemnation by the American Medical Association.[21]

Nutrition Immediately Preceding and During Competition

While evidence concerning possible special nutritional requirements of athletes is at most meager, there are a number of rules which have been found useful by competent, objective physicians ministering to college teams,[22] particularly those involved in long-duration events such as marathons. The essential objective is that nutrition should not interfere with competitive performance and its attendant physical and psychologic stresses.

Water balance—The requirements for salt can be met in a quantitative fashion by ingestion of bouillon at least three hours before a competitive event. If thirst ensues, it should happen no less than one and one-half hours before the event. Ingestion of water at that time will still permit elimination of excess fluid before the competition.

Carbohydrate loading—There is a strong presumption that for long-distance events carbohydrate is a better fuel than is fat or protein. Increasing carbohydrate reserves can be done simultaneously by two methods. (1) Exercise should be tapered off 48 hours before competitive effort, and the athlete should rest 24 hours before the event. (2) The last meal eaten before the event should be one high in carbohydrate, such as cereal (oatmeal), toast, jam or honey, etc.

Avoidance of proteins, bulky foods, etc.—The problem of the need for urinary or bowel excretion during a competitive event can be serious or even disabling. Proteins are a source of fixed acids which can be eliminated only by urinary excretion. Protein intake is therefore best reduced to the minimum at the meal preceding the event. Similarly, bulky foods (high cellulose foods, such as lettuce, and seed-containing vegetables, such as tomatoes) are best eliminated from the diet during the 48 hours preceding contests. Highly spiced foods also should be avoided during this period.

Tea, coffee, alcohol—It has been pointed out that these writers take a moderate view concerning alcoholic beverages, tea and coffee. There is no evidence that small amounts of these in the training diet are harmful. On the other hand, there is good reason to avoid them just before a contest. Alcohol, even in small amounts, may have some effect on coordination. Coffee and tea, while stimulants, may have a depressing effect three or four hours later and thus impair performance if consumed at the meal preceding exercise.

Nutrition during contests—Some sugar feeding during a long and exhausting contest does improve performance. Feeding glucose pills, pieces of sugar, or honey, however, tends to draw fluid for their digestion and absorption into the gastrointestinal tract and further dehydrate the organism. The subject may be fed lightly with strongly sweetened tea with lemon, which does not cause this difficulty.

Conclusions

The evidence presented in this article indicates clearly that the optimal diet for an athlete is not different in any major respect from that which would be recommended to any normal person. The diet should be adequate for maintenance, for growth if the person is still growing, for increase in muscle mass if necessary, and for fulfilling the energy requirements corresponding to the athlete's physical activity. Special attention might be given to the weight of the athlete in terms of desirability of possible gain or loss. When loss is indicated, crash diets should be avoided. Increased physical activity usually means that with moderate dietary controls, fat can

be lost efficiently and relatively painlessly. If an increase in muscle mass occurs at the same time, the effect on weight of loss of fat may be counterbalanced by gain in body protein. Evolution of body composition can be followed by observation, caliper measurements, and by the determination of such indexes as waist circumference.

In general, it appears that athletes should not eat less than three meals a day. When the sports practiced are particularly protracted and exhausting, up to five lighter meals may be a preferable pattern. Available evidence indicates that the relative composition or size of the meal preceding an athletic event of short duration has little influence on performance. (A reasonable delay should elapse between the meal and the competitive event.) However, there is also evidence showing that in sports requiring endurance and prolonged muscular work, performance is better maintained on a high carbohydrate diet than on a high fat diet (these are meant as the "usual" diet that is consumed for several days before an athletic event). In such cases, even the slight increase in efficiency with a high carbohydrate diet (the minimal figure of 5 per cent has been indicated by many investigators) may well prove decisive.

Wide variations of protein intake do not seem to influence performance. A well-balanced diet easily meets needs for maintenance and whatever muscle growth may take place. Large amounts of meat several times a day are unnecessary.

Supplementation of an adequate diet has not given clearly positive results. The multitude of problems encountered in the experimental design of studies purported to test the usefulness of supplements often has precluded ruling out the effects of motivation and progressive training. It is probable that hard muscular exercise does increase the need for some of the B complex vitamins, but in a balanced diet such increased needs should be met by the increase in food intake secondary to intense exercise.

The value of corn oil and vitamin E has not been definitely demonstrated. The use of ergogenic supplements such as gelatin and phosphate has not given unequivocal results. Athletic performance per se does not increase the need for salt. Salt supplementation (food salting, salted bouillon, or tablets) is necessary only if considerable sweating occurs during the beginning of training, under vigorous climatic conditions, or with prolonged exertion.

The use of alcohol, coffee, tea or other beverages containing caffeine should be restricted to small amounts.

It thus appears that nutritional requirements of athletes are essentially similar to those of nonathletes, except in regard to amounts (which should be regulated normally by appetite) and in the avoidance of excessive amounts of fat, particularly in sports entailing protracted heavy physical activity. The practice of feeding athletes at training tables may have some justification of convenience. Athletes often start practice before colleges reopen; the sports schedule may be such as to necessitate different hours for mealtime. There may also be some justification for this practice from the psychologic standpoint, in that it may help to create a "team spirit." By the same token, some educators dislike the segregation of athletes which thus takes place and consider that the training tables decrease the opportunity for conversing with greater numbers of students. Certainly, there is no *nutritional* justification for training tables at present. The normal fare of schools and colleges should be wholesome and adequate for all students. Extra needs of athletes can be taken care of by second or third portions and increased bread consumption.

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AUTHORS' NOTE: All references before 1942 have been omitted. A good review of the literature before that time is reference No. 9.

Scientific Exhibit

Chemotherapy in Rheumatoid Arthritis

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RHEUMATOID arthritis is a complicated and variable disease of unknown etiology. No therapeutic agent or combination of agents is completely efficacious in all instances. The program of medical therapy presented here begins simply with an analgesic, and becomes increasingly complex depending on the severity of the disease. A program of physical medicine, including exercises to strengthen muscles and maintain the normal range of motion in affected joints, is provided for all patients.

Exhibit designed and executed by The Department of Medical Illustration, The Frank E. Bunts Educational Institute.

Medical Therapy

Salicylates

Patients with early or nonprogressive disease who are able to maintain moderate activity are given only a salicylate preparation (3 to 8 gm. daily) and daily physical therapy. Subjective and objective response to treatment is evaluated at six to eight week intervals. If the disease progresses, one of the 4-aminoquinoline drugs is substituted for or combined with the salicylate preparation.

Hydroxychloroquine Sulfate or Chloroquine Phosphate

The 4-aminoquinoline drugs are administered to patients who do not respond satisfactorily to salicylates and to those who have more active disease. The usual dosage of hydroxychloroquine sulfate (PLAQUENIL® sulfate) is from 400 to 600 mg. daily, and of chloroquine phosphate (ARALEN® phosphate) 250 mg. daily. Because the response to these agents sometimes is delayed or incomplete, supplementary doses of other therapeutic agents (salicylates, corticosteroids, or amine-oxidase inhibitors) often are prescribed in amounts which if taken alone would be too small to cause significant improvement.

Combinations of Drugs

For patients incapacitated by persistently active disease, for those in relapse whose disease has resisted all previous treatment, and for those exhibiting exogenous hypercortisonism, a program of therapy has been devised in which certain combinations of drugs are administered. The drugs selected and the routes of administration vary depending on the severity of the disease, extent of inflammatory and destructive joint manifestations, emotional state of the patient, and response to previous therapy. The drugs are classified as follows: those used for initial induction of suppression of disease activity (ACTH and nitrogen mustard); those used to maintain the suppressed state (4-aminoquinoline drugs and small doses of a corticosteroid); and those used to influence the central nervous system manifestations (amine-oxidase inhibitor).

Induction therapy

Intravenous administration of ACTH and nitrogen mustard in recommended doses is a quick, safe method of inducing suppression of the mesenchymal inflammatory reaction in rheumatoid arthritis. Ten units of an aqueous preparation of ACTH diluted in 500 or 1000 ml. of 5 per cent dextrose in water is infused over a period of four hours. An antiemetic drug is given at the beginning of the infusion; one-half hour later, 2 mg. of nitrogen mustard diluted in 2 ml. of saline solution is injected directly into the intravenous tubing. Intravenous therapy is continued for from 5 to 10 days depending on the patient's response. After five days of intravenous therapy, the dose of nitrogen mustard is reduced to 1 mg. This treatment is most effective in suppressing swelling of the soft tissues, fever, constitutional symptoms, and acute or subacute inflammatory swelling of joints. The suppressive effect is of short duration; symptoms usually reappear in from four weeks to three months if maintenance therapy is not instituted at the start of induction therapy.

Oral maintenance therapy

A 4-aminoquinoline drug such as hydroxychloroquine sulfate (200 mg. three times daily) or chloroquine phosphate (250 mg. daily) is used for oral maintenance therapy, and its administration is begun simultaneously with the ACTH and nitrogen mustard intravenous therapy. Prednisone or an analogous derivative (1 to 2.5 mg. three times daily) is administered temporarily. This combination of orally administered drugs is continued until the patient is practically free of symptoms, usually for from 3 to 12 months, and then the dose of corticosteroid is reduced and the drug is stopped. Exacerbations usually diminish or disappear after the first year of maintenance therapy with one of the 4-aminoquinoline compounds. However, it is usually necessary to continue treatment with one of these drugs as long as there is laboratory evidence of disease activity.

Intramuscular ACTH

Long-acting ACTH supplements the maintenance chemotherapeutic program of patients with progressive disease and those who previously received large doses of corticosteroids. The usual dosage is 10 units injected intramuscularly once or twice weekly for three to six months. The patient is instructed in the technic of self-administration. ACTH is withdrawn when significant improvement has occurred and the disease has stabilized.

Amine-oxidase inhibitor

We believe iproniazid (MARSILID® phosphate) or a related compound is especially useful as a temporary adjunct to therapy for patients with various degrees of depression and emotional instability. Irrespective of the program of therapy selected for the patient, iproniazid may be administered in a dosage of 50 mg. once a day for a few weeks, after which the dosage may be reduced gradually to 10 mg. daily or every other day. Response to the drug usually is rapid, and toxicity has not been apparent with this dosage schedule. When the patient has gained in weight and when strength and a sense of well-being have returned, the drug can be stopped.

Intra-articular therapy

Joints which have been inflamed for years may have thick formation of pannus and varying degrees of effusion, and may respond incompletely to oral and parenteral therapy. Increasing the dosage of the oral medication usually will only produce toxic reactions. Intra-articular injections of hydrocortisone or a related steroid are of value when this problem exists, but often their effect is only temporary (from three days to three weeks). To prolong the effect of intra-articular therapy in the larger joints with thick pannus, small doses of nitrogen mustard (0.5 mg. diluted in 0.5 ml. saline solution) are mixed with hydrocortisone acetate (25 mg. or 1 ml.). This combination is safe and prolongs suppression of inflammation in knees and ankles, which in many instances have been relieved for only a few days or weeks by intra-articular administration of hydrocortisone alone. When there are severe chondromalacia of the patella, advanced destruction of cartilage, and absence of fluid formation within the joint, the injections consist solely of a hydrocortisone preparation.

This program of therapy can be modified easily for each patient depending on the manifestations of his disease and the time treatment is started. As improvement occurs, the drugs are withdrawn in an orderly fashion and maintenance therapy is continued with a 4-aminoquinoline compound.

Important Considerations

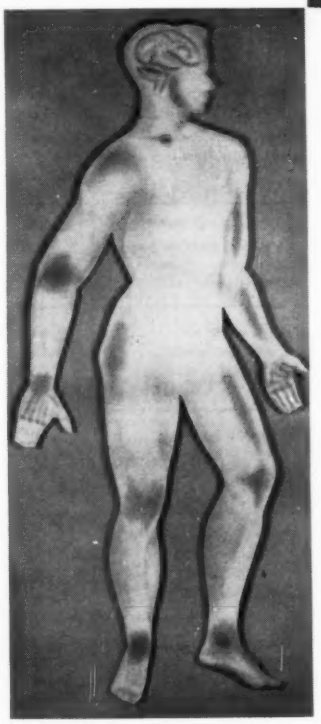
Rheumatoid arthritis is a variable and unstable disease involving multiple systems for which control therapy is individualized.

Chemotherapy is considered a supplement to measures of proved value, which include limitation of activity, physical therapy, orthopedic measures, and treatment of associated disease states.

Combined therapeutic agents, with individual pharmacologic actions, used in small doses usually result in greater, more prolonged suppression of inflammation and fewer toxic reactions.

A combined, flexible drug program can be adjusted according to the disease state while steroid therapy is used sparingly and temporarily.

Disease Manifestations



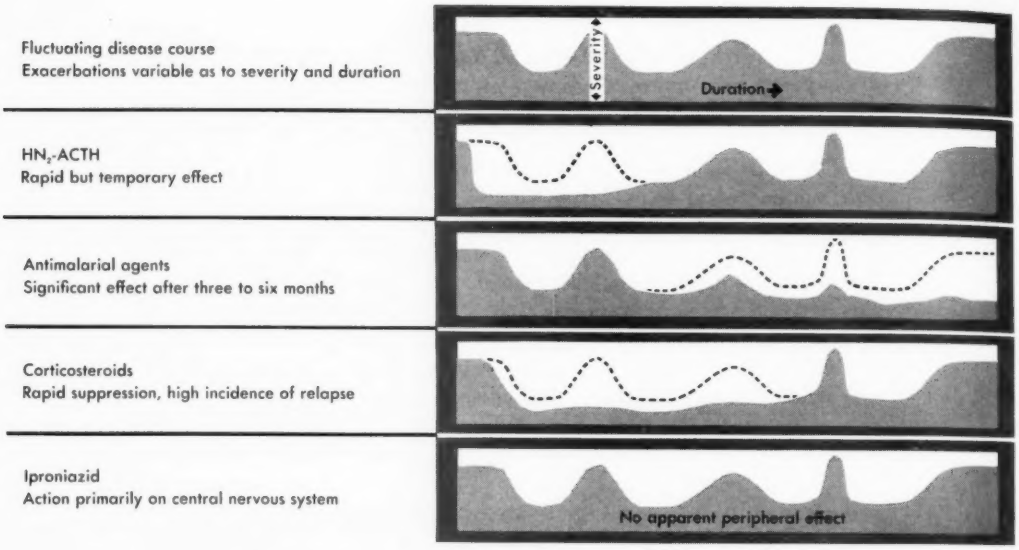
Central nervous system

- Depression
- Instability
- Fatigability
- Anorexia
- Sweating
- Vasomotor reactivity
- Muscle atrophy
- Decreased tendon reflexes

Mesenchymal tissue

- Inflammation
- Fibrous tissue proliferation
- Nodule formation
- Muscle atrophy

Drug Response on Objective Disease Manifestations



THERAPEUTIC AGENT	KNOWN ACTION	DESIRABLE FEATURES	UNDESIRABLE FEATURES
Nitrogen mustard	Alkylating agent	Inflammation rapidly suppressed	Temporary effect lasting four to six weeks. Potentially toxic drug in large doses
Aqueous corticotropin	Stimulates adrenal cortex	Acts synergistically with nitrogen mustard causing rapid suppression of mesenchymal inflammation	Hyperadrenocorticism results from overdosage
Chloroquine phosphate or hydroxychloroquine sulfate	Histamine liberator	Low incidence of toxicity. Long-term administration results in lessened disease activity	Improvement appears slowly (one to three months). Suppression of inflammation may be incomplete
Iproniazid	Amine-oxidase inhibitor	Alleviates central nervous system manifestations, often essential in rheumatoid arthritis	Cumulative drug overdosage results in central nervous system hyperactivity. Joint inflammation is not suppressed
Repository corticotropin	Stimulates adrenal cortex	Stabilizes disease activity	Hyperadrenocorticism results from overdosage
Prednisone	Delays connective-tissue proliferation	Mesenchymal reaction rapidly suppressed	Hypercortisonism. High incidence of relapse

Combined Chemotherapy

Systemic

Iproniazid for central nervous system manifestations.

Mesenchymal tissue.

1. Rapid suppression of mesenchymal inflammation—HN_2, 2 mg., and ACTH, 10 units, intravenously daily for five to seven days.
2. Maintenance of suppressed state
   —Hydroxychloroquine sulfate, 0.6 gm., or chloroquine phosphate, 0.25 gm. (anti-inflammatory).
   —Prednisone, 3 to 7.5 mg. (anti-inflammatory, fibroblastic proliferation reduced).

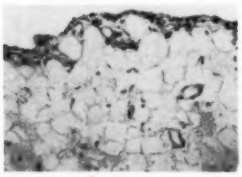
Local

Intra-articular and extra-articular injections result in prolonged reduction of both inflammation and fibroblastic proliferation.

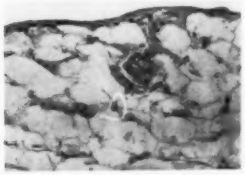
Hydrocortisone (acetate or tertiary butylacetate) in tendons, muscles, carpal tunnel and small joints.

Hydrocortisone-nitrogen mustard (usual mixture, 25 mg. hydrocortisone and 0.5 mg. HN_2) in large joints and nodules.

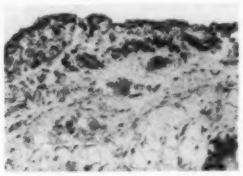
Effect of Nitrogen Mustard on Canine Synovialis



Normal canine synovial membrane.

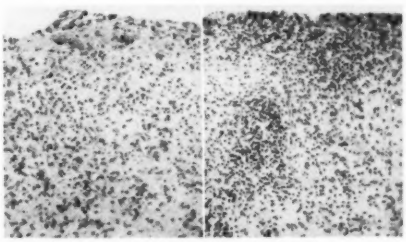


Two days after injection of 0.5 mg. HN_2.

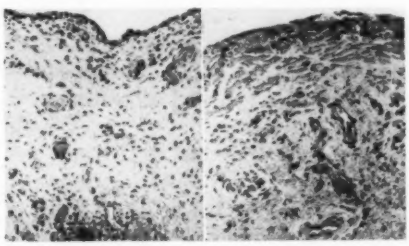


Thirty days after injection of 1 mg. HN_2.

Effects of Nitrogen Mustard on Rheumatoid Arthritis

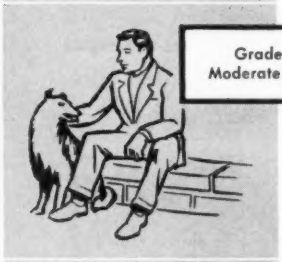


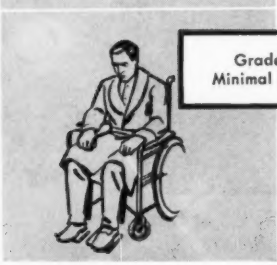
Acute rheumatoid arthritis before treatment with intra-articular HN_2.



One month after 1 mg. HN_2 x 3 at three day intervals.

Results of Treatment





Classification of Disease	Therapeutic Agent
I. MILDLY ACTIVE (Stage I-IV, functional capacity I) 70 PATIENTS TREATED 6 Patients 26 10 28 0 10 20 30 40 50	Sodium salicylate (4 to 6 gm. daily) THERAPEUTIC RESPONSE GRADE I — Excellent, asymptomatic, sedimentation rate normal. II — Good, minor aches and pains. III — Fair, slight persistence of joint tenderness and swelling. IV — Poor, moderate persistence or no relief of pain and swelling.
II. MODERATELY ACTIVE (Stage I-IV, functional capacity II-III) 26 PATIENTS TREATED 8 Patients 7 5 6 0 10 20 30 40 50	Hydroxychloroquine sulfate (0.6 gm. daily) GRADE I II III IV
III. PROGRESSIVE DISEASE (Stage I-IV, functional capacity II-III) 25 PATIENTS TREATED 4 Patients 5 8 8 0 10 20 30 40 50	Chloroquine phosphate (0.25 gm. daily) GRADE I II III IV
IV. PERSISTENT OR PROGRESSIVE DISEASE WITHOUT ADVANCED JOINT DESTRUCTION (Stage II-III, functional capacity III-IV) 254 PATIENTS TREATED 97 Patients 126 24 7 0 10 20 30 40 50	Combined therapy GRADE I II III IV • I.V. ACTH-HN_2 • Intra-articular HN_2-hydrocortisone • Antimalarial-corticosteroid • Iproniazid • Repository ACTH
V. PERSISTENT OR PROGRESSIVE DISEASE COMPLICATED BY ADVANCED JOINT DESTRUCTION 67 PATIENTS TREATED 8 Patients 15 30 14 0 10 20 30 40 50	GRADE I II III IV • I.V. ACTH-HN_2 • Intra-articular hydrocortisone • Antimalarial-corticosteroid • Iproniazid • Repository ACTH

CLINICAL STUDY

Clinical Evaluation of Ethoheptazine in the Management of Postpartum Pain

W. DUANE McCARTY AND JOHN C. ULLERY*

Ohio State University College of Medicine, Columbus

The combination of ethoheptazine citrate and acetylsalicylic acid produced satisfactory relief of postpartum pain in more than 90 per cent of a series of 227 unselected patients, without the addiction liability of other analgesic agents. In six of eight cases of confirmed postspinal headache the combination afforded moderate relief. Side effects were infrequent, and in no case did untoward reactions necessitate discontinuation of treatment.

THIS study was made to evaluate the clinical effectiveness and the incidence of side effects of a combination of ethoheptazine citrate and acetylsalicylic acid (ZACTIRIN®) to relieve pain in the immediate postpartum period.

Ethoheptazine is a racemic mixture of the d and l isomers of 1-methyl-4-carbethoxy-4-phenyl hexamethylenimine. Previous clinical studies and investigations have indicated the moderate analgesic properties of ethoheptazine,[1,2] and have shown that it produces fewer side effects than other agents,[2,3] controls postpartum pain in the majority of cases,[2] lacks addiction potential,[4] and produces minimal or no sedation.[3] Cass and associates established that ethoheptazine combined with acetylsalicylic acid possesses an analgesic effectiveness comparable to 30 mg. of codeine and 10 gr. acetylsalicylic acid.

Method

We were especially interested in comparing the combination of ethoheptazine and acetylsalicylic acid with a combination of codeine and aspirin, which frequently is used to relieve postpartum pain on our obstetric service. In this study, ethoheptazine and acetylsalicylic acid (Zactirin) was substituted for the codeine-aspirin combination in all cases in which an analgesic agent of that strength seemed to be indicated.

No attempt was made to select patients for the study. Postpartum patients were included at random from the ward service at University Hospital from June 15, 1958 to September 1, 1958, without selection as to type, severity or duration of postpartum pain.

Response to treatment was measured in three ways: extent of relief of pain, evidence

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JOHN C. ULLERY

of side reactions, and average dosage required to keep the patient comfortable. As in a similar study conducted by Batterman and associates,[2] clinical response was graded as "acceptable" when the patient received "complete" or "moderate" relief. Complete analgesia constituted subjective relief of pain for three or more hours without untoward reaction. Moderate response was partial relief (50 per cent or more) for three or more hours or complete relief for more than two but less than three hours, also without significant untoward effects. Only slight analgesia was considered an "unsatisfactory" response; the response also would have been graded as unsatisfactory if untoward side reactions had required termination of the use of the drug. In some instances there was an adequate response initially but an unfavorable response with continued therapy, and these were graded as unsatisfactory.

A total of 227 unselected ward patients from the clinical obstetric service at University Hospital were included in the study group. Their ages ranged from 17 to 39 years. The routine dosage was 2 tablets every four hours as needed.*

The initial dose was given only after the patient requested medication to relieve pain. The drug's effectiveness was evaluated from the observations by the house officers and the nurses in attendance, and the response was judged only after all impressions were recorded. Patients were observed for untoward reactions such as nausea, vomiting, epigastric distress, dizziness, listlessness and pruritus, and any other side effects reported voluntarily by the patient were also noted.

*Clinical supplies of Zactirin tablets containing 75 mg. ethoheptazine citrate and 325 mg. (5 gr.) acetylsalicylic acid were made available by Wyeth Laboratories.

Results

The 227 women each received 150 mg. ethoheptazine citrate and 650 mg. (10 gr.) acetylsalicylic acid (2 Zactirin tablets) every four hours as needed for pain in the immediate postpartum period. The total number of doses in each case ranged from 1 to 14; approximately 1300 doses were administered to all the patients (table 1).

Satisfactory relief of perineal pain or abdominal cramping was achieved in 91.3 per cent of patients complaining of one or both types of pain. Of considerable interest is the "moderate" relief of postspinal cephalalgia in six of eight patients who complained of this type of pain; the obstetric anesthesiology service confirmed the diagnosis in all eight cases.

Table 2 presents data on the types of pain treated and the degree of relief which was obtained. Treatment was effective in 91 per cent of the cases and "unsatisfactory" in only 9 per cent.

The over-all incidence of side reactions was 4.8 per cent. Nausea was the complaint in 1.8 per cent, dizziness in 1 per cent, drowsiness in 1 per cent, epigastric distress in 1 per cent, and pruritus in 0.5 per cent.

TABLE 1

DOSAGE OF ZACTIRIN IN TREATMENT OF POSTPARTUM PAIN

TYPE OF PAIN	NUMBER OF PATIENTS	TOTAL NUMBER OF DOSES		
		1-3	*4-6*	*7 or more*
Afterbirth pain	179	50	86	43
Episiotomy	29	9	14	6
Postspinal headache	8	3	3	2
Other headache	2	1	1	
Breast engorgement	2	1		1
Hemorrhoids	3	2	1	
Calf pain	1	1		
Back pain	1			1
False labor (cramps)	2	2		

TABLE 2

EFFECTIVENESS OF ZACTIRIN IN TREATMENT OF POSTPARTUM PAIN

TYPE OF PAIN	NUMBER OF PATIENTS	PATIENTS COMPLETELY RELIEVED		PATIENTS MODERATELY RELIEVED		TOTAL PERCENTAGE OF PATIENTS RELIEVED	PATIENTS UNSATISFACTORILY RELIEVED	
		Number	*Per cent*	*Number*	*Per cent*		*Number*	*Per cent*
Afterbirth pain	179	97	54	68	38	92	14	8
Episiotomy	29	2	7	23	79	86	4	14
Postspinal headache	8	0	0	6	75	75	2	25
Other headache	2	1	50	1	50	100		
Breast engorgement	2	1	50	1	50	100		
Hemorrhoids	3	2	66	1	33	100		
Other pain	4	2	50	2	50	100		
Calf pain	1							
Back pain	1							
False labor (cramps)	2							

Observations

1. "Satisfactory" analgesia in postpartum pain can be achieved in more than 90 per cent of patients treated with a combination of ethoheptazine and acetylsalicylic acid.
2. There were *no* untoward reactions which necessitated discontinuing treatment.
3. Side effects were quite infrequent and not of major significance.

Conclusion

The combination of ethoheptazine and acetylsalicylic acid has a low incidence of untoward reactions and produces consistent relief of most types of postpartum pain. It is a valuable addition to the armamentarium of analgesic agents and perhaps is the answer to the challenge of these criteria.

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CLINICAL STUDY

Diuretic Effects of Flumethiazide, a Benzothiadiazine Derivative

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Hahnemann Medical College and Hospital, Philadelphia

Flumethiazide is a potent diuretic agent which may be safely administered to cardiac patients.

Both short-term and long-term studies of a large group of patients with congestive heart-failure showed that flumethiazide produced no significant change in the glomerular filtration rate, renal plasma flow or blood pressure.

Bio-assay studies revealed that flumethiazide produced a marked natruretic effect. With a therapeutic dose of from 200 to 2000 mg., the sodium excretion in response to flumethiazide was similar to that resulting from administration of chlorothiazide.

REGARDLESS of their origin, the common states of edema are associated with the excessive retention of sodium and water. The recent introduction of chlorothiazide as a potent, orally administered saluretic agent has provided improved control of edema in ambulant patients and has stimulated intense interest in other derivatives of the benzothiadiazine structure. This report is a summary of our investigation of trifluoromethylthiazide (flumethiazide† [ADEMOL®]).[1,2] Flumethiazide differs from chlorothiazide in that a trifluoromethyl group has been substituted for the chloride atom (figure 1). Minimal changes in the basic structure have produced marked changes in the potency of other groups of drugs; therefore, the attempts at modifying the original structure of chlorothiazide have been a logical sequence of the investigation of diuretics.

MORTON FUCHS

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†Supplied by E. R. Squibb & Sons, division of Olin Mathieson Chemical Corp., New York.

Methods and Materials

Clinical studies—Forty-eight hour study—In our diuretic clinic, we determined the 48

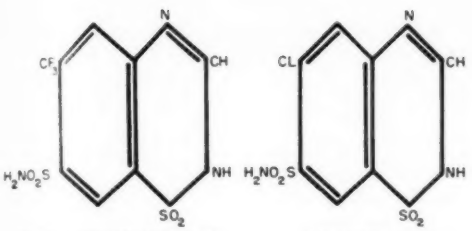


FIGURE 1. Structural formulas of chlorothiazide and flumethiazide.

hour weight loss produced by various-sized doses of flumethiazide administered to patients with mild to moderate congestive heart-failure. These patients were equally divided according to sex, and their ages ranged from 42 to 68 years. They were on a maintenance dosage of digitalis, and they required mercurial injections once or twice a week in order to maintain a dry weight and to remain free of symptoms of congestive failure. The sodium intake was not controlled because of the socioeconomic status of this group. Coronary artery disease and chronic rheumatic valvular disease were the predominant causes of congestive heart-failure. Diuretic therapy was withheld for one week between doses of the drug, while other therapy remained unchanged. The patients were weighed before breakfast and after voiding; they were weighed again after having received the drug for the two day period. The drug was administered in dosages of 400, 800 and 1000 mg. twice daily and 1000 mg. three times daily. Comparative studies were made with 20 mg. chlormerodrin (NEOHYDRIN®*), administered four times daily, and with 500 and 1000 mg. chlorothiazide (DIURIL®†), administered twice daily. The same procedure was followed with each drug studied.

Five week study—Many patients in the diuretic clinic were evaluated over a five week period. During this time, 1000 mg. flumethiazide was administered twice daily. The patients were examined and questioned twice a week for evaluation of clinical response, cardiac compensation and any side effects. Before this study was initiated, diuretic therapy was withheld for one week, so that serum electrolytes stabilized. Serum electrolyte concentrations, as well as complete blood counts, were determined before and at the end of the study. The electrolyte determinations included serum sodium, potassium, chloride, carbon dioxide-combining power and blood urea nitrogen; the blood counts included hemoglobin, hematocrit, white blood cell count and differential. Weights were recorded twice a week.

Bio-assay studies—The total 24 hour urinary excretion of sodium in response to increasing doses of flumethiazide was determined in four patients. These patients were in a state of myocardial compensation, so that no overt physical findings of congestive heart-failure or edema were evident. Renal function was normal. The daily 24 hour sodium intake was limited to 50 mEq., and fluid intake was limited to from 2000 to 3000 cc. daily. Twenty-four hour urine specimens were collected daily and analyzed for sodium and potassium, until constant control level of sodium excretion was obtained. Flumethiazide was then administered in a dosage of 100, 200, 400, 800, 1000, 2000 and 3000 mg. daily for two days. A period of equilibration, without diuretics, was allowed between each dose of the drug in order for the 24 hour urinary sodium excretion to return to control levels. The average increase in the 24 hour urinary sodium and potassium excretion for the two days during administration of the drug was then compared with control excretion. Five other cardiac patients under the same metabolic control, who were in a state of good myocardial compensation without edema, were given 800 mg. flumethiazide twice daily for six days after an initial control level of 24 hour urinary sodium excretion was established. The daily sodium excretion during administration of the drug was then compared with control excretion values.

Renal function and excretion studies—Renal function was studied in a group of seven patients who had been on a controlled regimen of 50 mEq. sodium and from 2000 to 3000 cc. fluid daily for several days. The glo-

*Supplied by Lakeside Laboratories, Milwaukee.

†Supplied by Merck Sharp & Dohme, division of Merck & Co., Inc., Philadelphia.

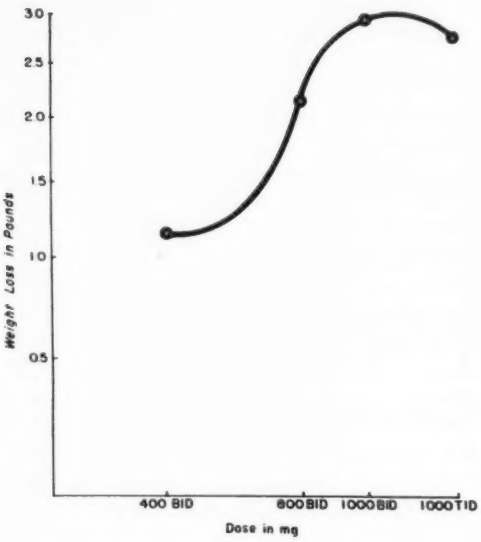


FIGURE 2. Weight loss resulting from increasing doses of flumethiazide.

(Courtesy of Fuchs, M., Bodi, T. and Moyer, J. H.[1])

merular filtration rate and renal plasma flow were determined by the standard insulin and para-aminohippuric acid clearance technics described by Roe and associates[3] and by Smith and co-workers.[4] The volume of urine and the sodium and potassium concentrations in the urine were determined during the renal clearance studies.

Three 20 minute collection periods for these studies were used to determine control levels. The patients were then given 800 mg. flumethiazide orally, and half-hourly and hourly collections were made for from four to seven hours. Determinations of volume of urine, renal hemodynamics, and serum and urinary electrolyte excretions were then made as for control periods. One patient in this group also received 2000 mg. flumethiazide orally one week after this study. Except for the dose, the experiment was the same as was previously described.

Results

Response in the 48 hour study—The 48 hour weight loss in 13 patients receiving 400 mg. flumethiazide twice daily was 1.4 lb. ($p = <0.001$). In 20 patients receiving 800 mg. flumethiazide twice daily, the weight loss was 2.3 lb. ($p = <0.001$), and it was 2.9 lb. ($p = <0.001$) in 13 patients receiving 1000 mg. twice daily. Ten patients lost an average of 2.3 lb. while receiving 1000 mg. flumethiazide three times daily ($p = <0.001$). Twenty-four patients receiving 500 mg. chlorothiazide twice daily lost 2.3 lb. ($p = <0.001$), and 22 patients lost 2.9 lb. with the administration of 1000 mg. chlorothiazide twice daily. Figure 2 shows the response to flumethiazide as determined by 48 hour weight loss. The maximal effective dosage was 2000 mg. daily:

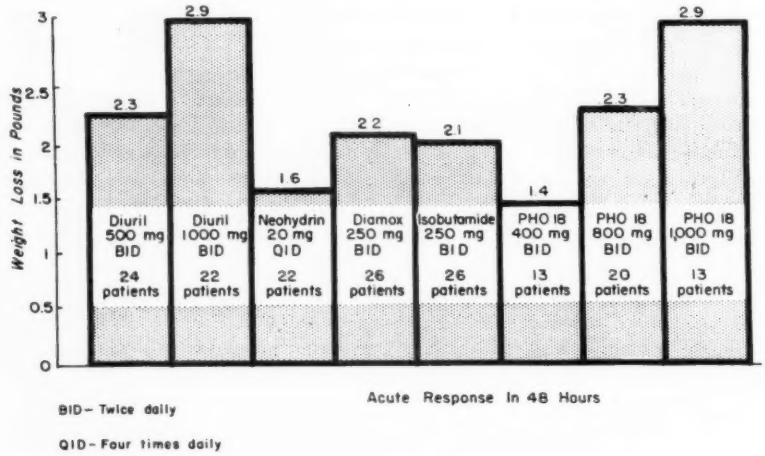


FIGURE 3. Comparative average weight loss produced by five orally administered diuretics given over a 48 hour period.

(Courtesy of Fuchs, M., Bodi, T. and Moyer, J. H.[1])

larger dosages had no further effect on weight loss over a short period. It would appear that the response to 500 mg. chlorothiazide administered twice daily is equivalent to the response to 800 mg. flumethiazide given twice daily (figure 3). However, analysis of the weight loss in response to administration of 500 mg. chlorothiazide twice daily and of 400 mg. flumethiazide twice daily revealed no statistically significant difference.

It must be noted that 13 patients who received flumethiazide showed no side effects and no change in blood pressure. At the end of the 48 hour period, the patients who were given flumethiazide in all dosage ranges had rather marked improvement from symptoms of heart-failure. The comparative effectiveness of the carbonic anhydrase inhibitor acetazolamide (DIAMOX®), of isobutamide, and of the orally administered mercurial chlormerodrin in producing a 48 hour weight loss also is shown in figure 3.

Results of five week study—Continuous oral administration of 1000 mg. flumethiazide twice daily to 18 of the clinic patients resulted in an average weight loss of 1.2 lb. ($p = <0.01$) at the end of the five week period. The patients remained free of symptoms of congestive failure and did not need additional mercurial diuretic therapy. There was no significant change in blood pressure; however, all but one of the patients in this study were normotensive.

The side effects experienced in this group of patients were insignificant; three patients had pruritus, and one had transient diarrhea and weakness. One patient with pruritus had similar complaints before receiving the drug. No rash was seen at any time, and the complaints of weakness and diarrhea could not be attributed to the drug. It was not necessary to discontinue use of the drug at any time during the study.

Results of the laboratory studies before and at the end of the five week period are shown in table 1. There was no significant change in the concentration of any electrolyte, and the complete blood counts were not influenced by the prolonged continuous administration of the drug.

TABLE 1

AVERAGE VALUES OF SERUM ELECTROLYTE CONCENTRATIONS IN 18 PATIENTS BEFORE AND AFTER TREATMENT WITH FLUMETHIAZIDE*

ELECTROLYTE	BEFORE THERAPY	AFTER THERAPY
Sodium (mEq.)	142	139
Potassium (mEq.)	4.7	4.1
Chloride (mEq.)	95	90
Carbon dioxide-combining power (mEq.)	22.8	19.3
Blood urea nitrogen (mg. %)	15	16

*Patients received 1000 mg. flumethiazide twice daily for five weeks.

Results of bio-assay studies—The sodium excretion in response to administration of flumethiazide is shown in figure 4. Natruretic activity appeared with a dose of 200 mg. and

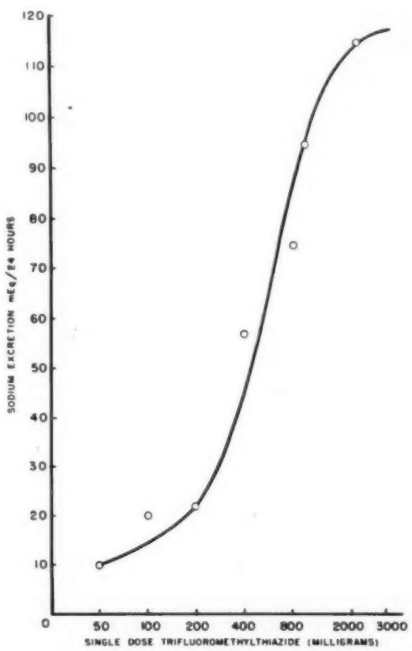


FIGURE 4. Sodium excretion resulting from administration of flumethiazide. Significant naturetic activity begins with a dose of 200 mg.; maximal effectiveness is achieved with a dose of 2000 mg.

rapidly increased with doses to the 2000 mg. level. This response curve is similar to that seen with administration of chlorothiazide.[5] Doses larger than 2000 mg. did not have a greater saluretic effect. Figure 5 shows the 24 hour urinary potassium excretion in response to administration of flumethiazide. Again, activity appeared to become prominent with a dose of 200 mg., but further increase in potassium excretion in response to larger doses was not of a significant degree. With lower doses of the drug in this group of patients, increase in potassium excretion appeared to be approximately one-half the amount of the increase in sodium excretion; however, with larger doses, increase in potassium excretion dropped to about one-third the amount of the increase in sodium excretion. With chlorothiazide, greater potassium excretion is stimulated with larger doses, in which the carbonic anhydrase activity is greater. Larger doses of flumethiazide do not significantly increase potassium excretion.

In five nonedematous patients who were given 800 mg. flumethiazide twice daily, 24 hour urinary sodium excretions obtained after the control study showed increase in sodium excretion on the first day; this gradually fell to control levels by the fourth day of treatment (figure 6). Water diuresis usually paralleled the sodium excretion in this study. Return of the 24 hour urinary sodium excretion to control levels probably implies a state of relative sodium depletion and the clinical state of dry weight and cardiac compensation.

Results of renal function and excretion studies—Results of the renal function studies are shown in figure 7. There was no significant change in the glomerular filtration rate, renal plasma flow, or blood pressure during the period of observation.

The effects of flumethiazide on the excretion of sodium and potassium and volume of urine are shown in figure 8. An increase in sodium excretion, seen during the second hour after administration of flumethiazide, persisted during the period of observation. Urine volume increased during the first hour of the study and remained elevated throughout the study. Potassium excretion remained relatively constant after administration of the drug and was not significantly elevated above control levels by the fourth hour of the study. Plasma sodium and potassium levels were not affected in this study.

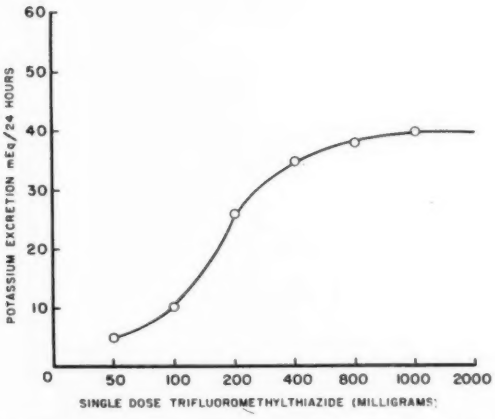


FIGURE 5. Potassium excretion resulting from administration of flumethiazide. Significant activity is observed with a dose of 200 mg., but it does not increase markedly with larger doses.

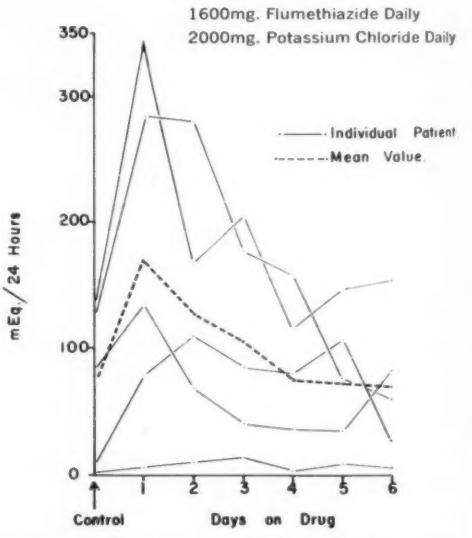
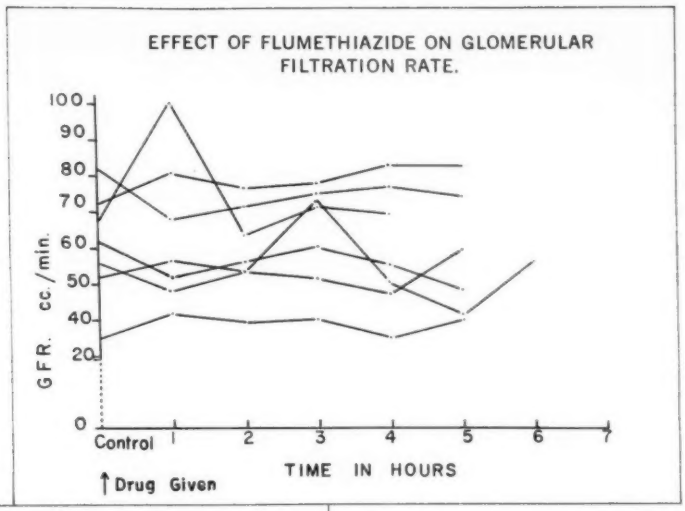


FIGURE 6. Effect of flumethiazide on daily sodium excretion. The sodium excretion falls to control levels by the fifth day of therapy; this condition probably represents relative sodium depletion and compensatory homeostatic mechanisms.

(Courtesy of Bodi, T., Fuchs, M. and Moyer, J. H.: Am. J. Cardiol. 4:464, 1959.)



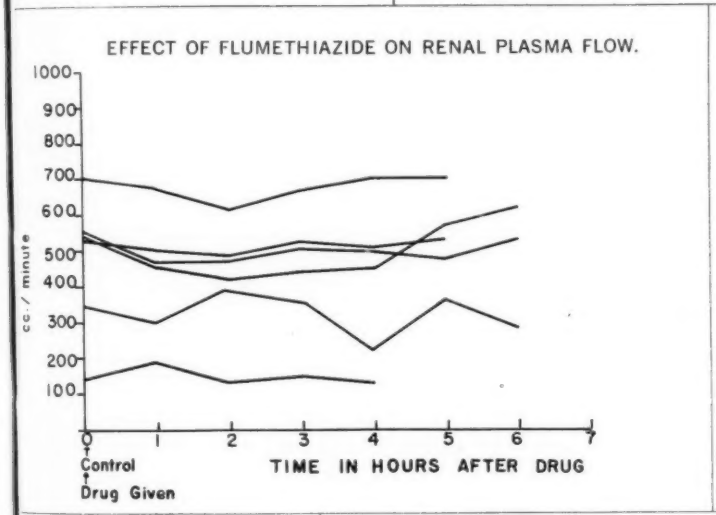
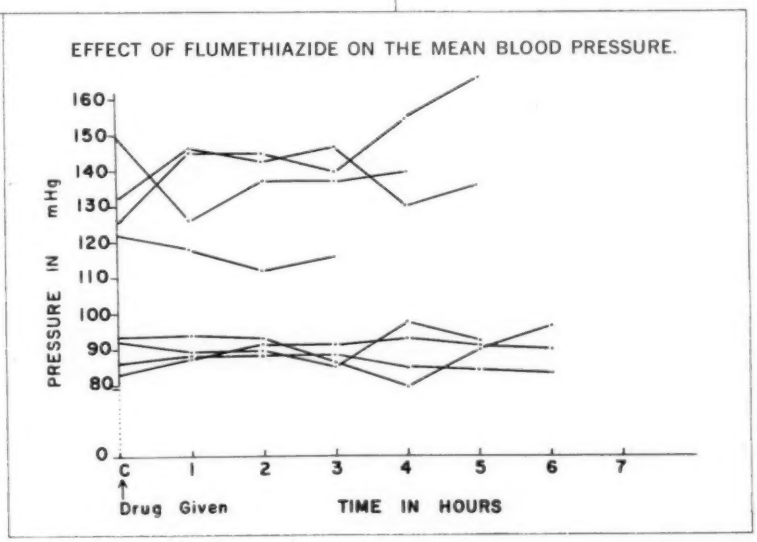


FIGURE 7. Effect of 800 mg. orally administered flumethiazide on glomerular filtration rate, renal plasma flow, and blood pressure.



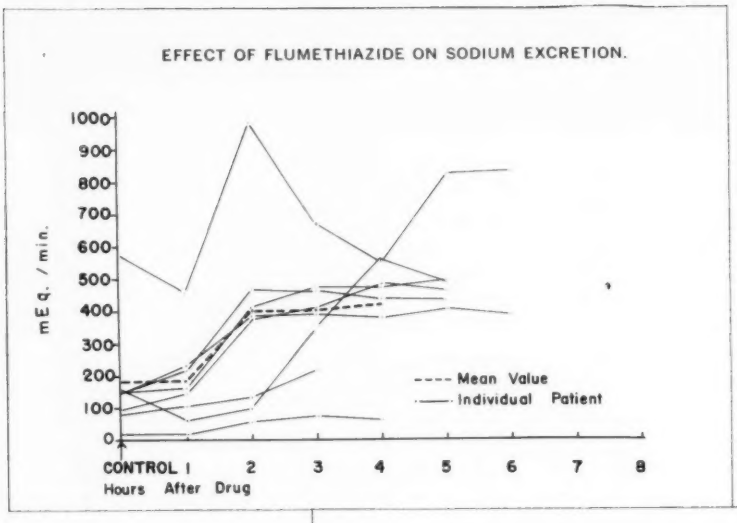
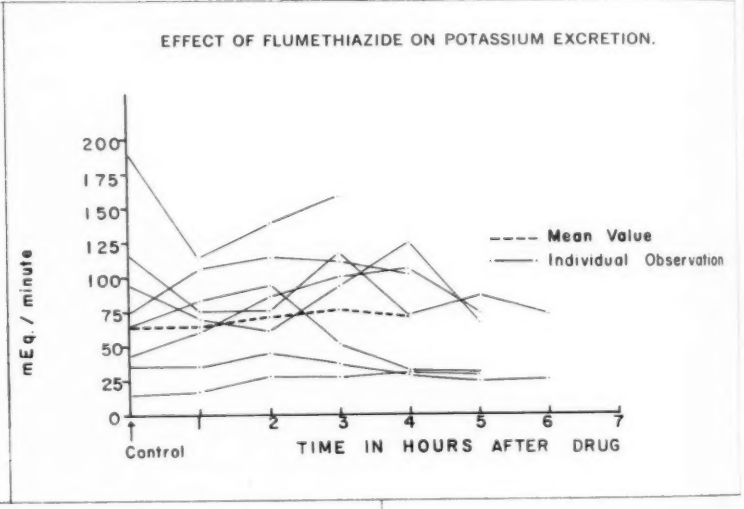
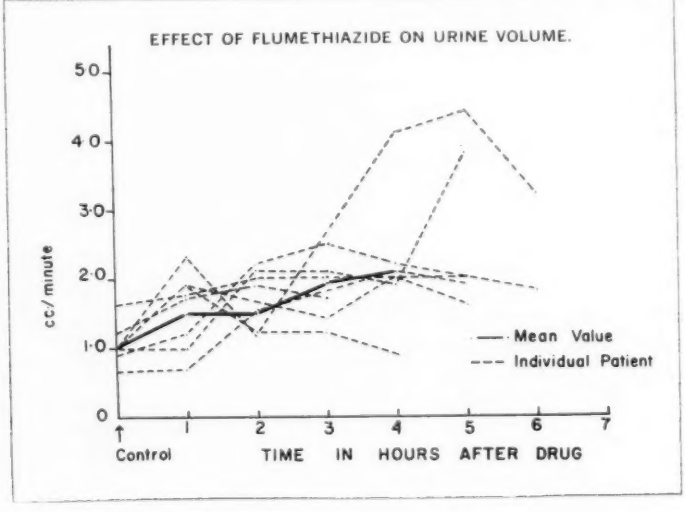
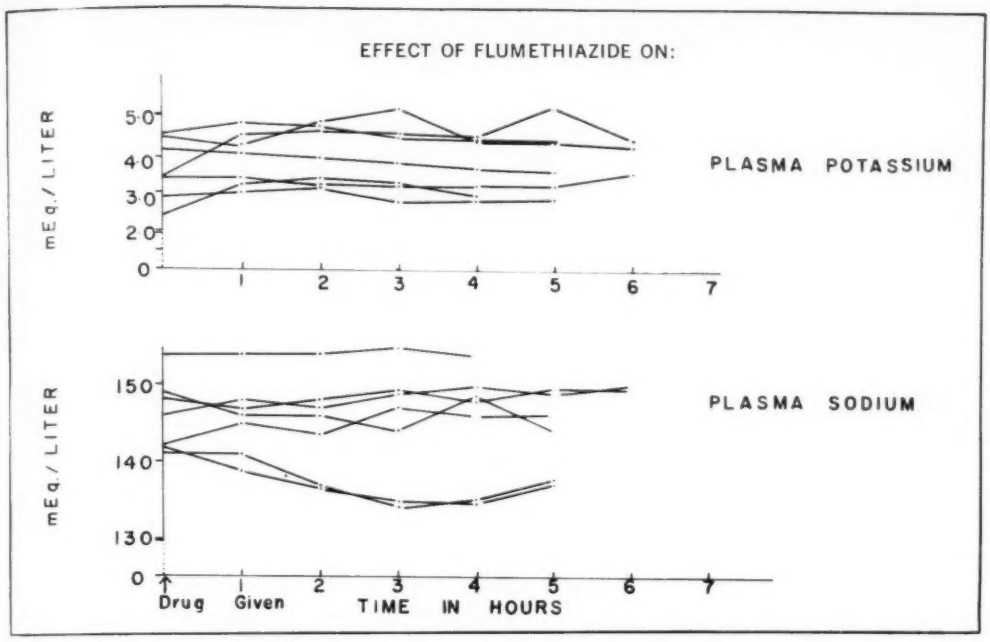


FIGURE 8. Effect of oral administration of flumethiazide on sodium and potassium excretion, the urine volume, and plasma potassium and sodium. The broken lines indicate observations on each individual patient; the heavy lines represent the mean average for all patients.





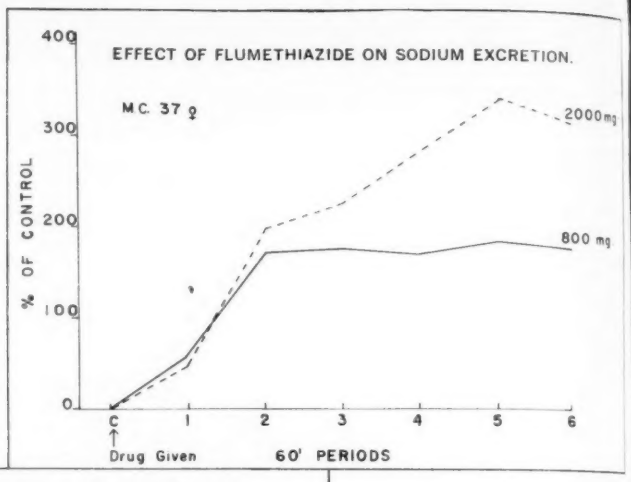


The comparative effects on renal hemodynamics and excretion resulting from administering both 800 and 2000 mg. flumethiazide to a representative patient are shown in figure 9. Sodium excretion increased during the second hour of observation with both doses of the drug, but the larger dose induced a correspondingly elevated natruresis. Potassium excretion did not increase significantly above control levels with either dose, and there was no apparent difference in the excretion produced by the two doses. Urine volume rose to a point more than twice as high as the control levels with the 2000 mg. dose and to nearly as high with the smaller dose, although the latter produced an effect of shorter duration. There was no influence on mean blood pressure, glomerular filtration rate, renal plasma flow or plasma sodium and potassium concentrations with either dose administered.

Discussion

Flumethiazide is an effective saluretic and diuretic agent which may be safely administered to cardiac patients over both long and short periods. There was no influence on renal plasma flow, blood pressure, or the glomerular filtration rate in a group of patients given orally administered doses of flumethiazide. The diuretic activity of this drug depends on its ability to block reabsorptive mechanisms at the renal tubular level. Its potency appears to equal that of chlorothiazide in establishing efficient clinical response in the ambulant cardiac patient, and sodium excretion in response to flumethiazide parallels that produced by similar doses of chlorothiazide. However, chlorothiazide and flumethiazide appear to differ in the lower dosage range when potency is judged by weight loss.

Weight response is a less sensitive index for comparing the two drugs than is a study of controlled sodium excretion. Since there appears to be little difference between the two drugs when potency is determined according to sodium excretion, the divergence of response with weight loss as the criterion probably should be discounted. The dosage range in the clinical application of flumethiazide is the same as that of chlorothiazide and approximately 10 times that of hydrochlorothiazide. (Hydrochlorothiazide has the same chemical



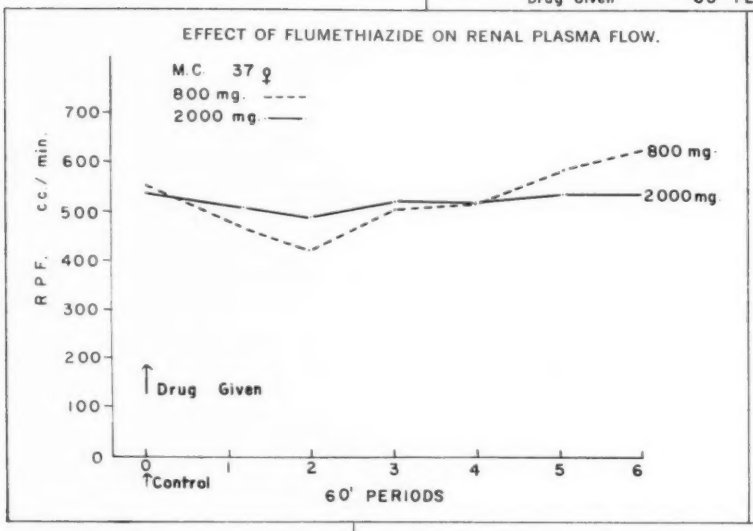
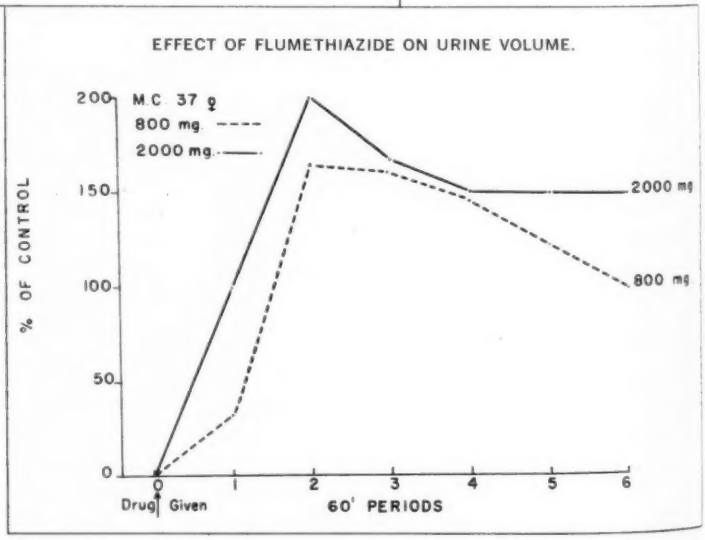
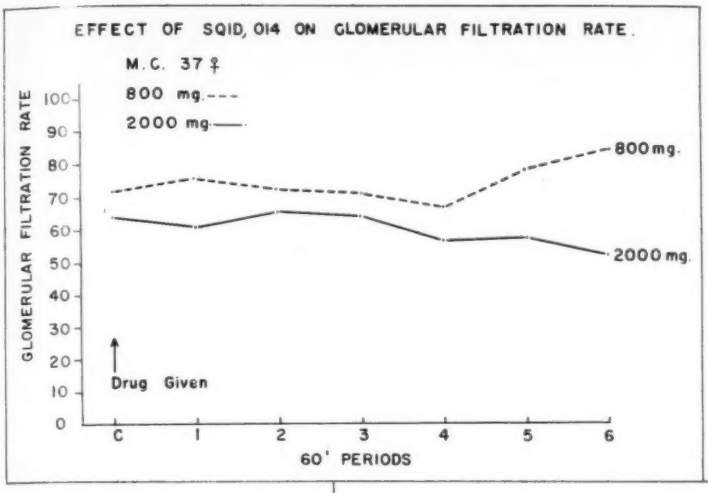
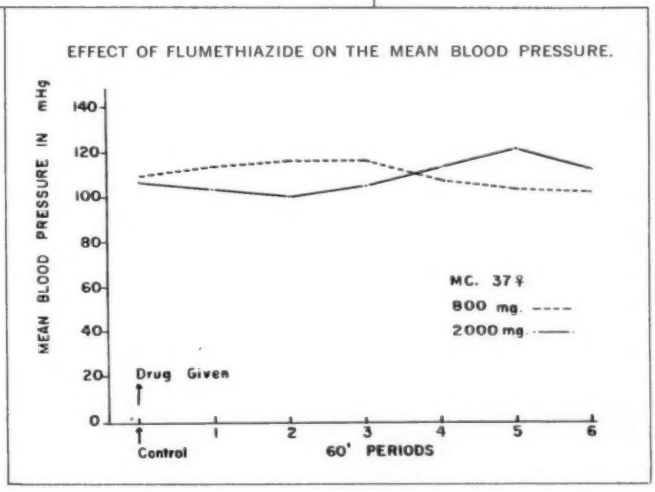


FIGURE 9. Comparative effects in one patient of doses of 800 and 2000 mg. flumethiazide on sodium excretion, renal plasma flow, urine volume, glomerular filtration rate, and mean blood pressure.







structure as chlorothiazide except for the saturation of the one double bond in the hetrocyclic ring by two hydrogen atoms.[5-8])

Although six hour observations after oral administration of flumethiazide over 48 hours revealed no significant change of potassium excretions above the control levels, an increase was seen in the 24 hour urine specimens. Potassium excretion produced by doses of flumethiazide larger than 200 mg. was not significantly greater than that produced by 200 mg. doses. However, potassium excretion is increased with large doses of chlorothiazide, in which the carbonic anhydrase activity of this drug becomes more manifest.

In this study, long-term administration of flumethiazide at high dosage levels produced no significant toxic side effects and no clinical evidence of electrolyte depletion or imbalance syndromes. Blood pressure was not affected by short-term or long-term administration of flumethiazide; however, the patients studied were not sufficiently hypertensive for any significant change in blood pressure to be noted. Long-term administration of flumethiazide produces an increased saluretic effect which falls to the control level in several days' time. The rapidity with which this fall occurs presumably depends on the amount of excess sodium stores; it probably would require more time to achieve this level in the edematous patient with large sodium stores than in the cardiac

patient who has good myocardial compensation. The fall to the control level represents a relative depletion of sodium and the attainment of dry weight as homeostatic compensatory mechanisms exert their influence. However, the possibility that a tolerance to these drugs may develop over a long period of continuous administration (two months or more) must still be more adequately evaluated.

Therapeutically, we have found that initial dosages of from 500 mg. once daily to 1000 mg. twice daily are highly satisfactory in producing a marked natruresis and diuresis in most edematous patients. Our observations have been concerned primarily with edema associated with congestive heart-failure. We have seen good results, however, in edematous patients with primary renal and hepatic disease, toxemias of pregnancy, and iatrogenic edematous states. The tendency of some patients to excrete excessive potassium is a potential hazard, and these patients should be observed closely. In such cases, the development of hypokalemia indicates that diuretic therapy should be discontinued and potassium replacement should be instituted.

We have found that initial and maintenance dosages of up to 1000 mg. flumethiazide twice daily generally have caused no electrolyte imbalance or unfavorable side effects. In guarding against low potassium syndromes, laboratory values are of secondary importance to close clinical observations. The presence of muscular weakness, gastrointestinal complaints and cardiac arrhythmias may signify a hypokalemic state. Frequent determinations of serum potassium levels and effects of supplemental potassium are valuable aids in diagnosing this condition. In the presence of a marked hypokalemia, it is mandatory to withhold temporarily diuretics of the benzothiadiazine group. In routine use of flumethiazide, however, patients receiving an adequate diet are instructed to take one or two glasses of fruit juice daily, and supplemental potassium is not required. Close clinical observation of patients on the previously mentioned regimen has shown flumethiazide to be a safe and effective diuretic agent comparable in effectiveness to chlorothiazide.

Summary

1. A clinical evaluation of trifluoromethylthiazide (flumethiazide) as a diuretic agent is presented. This drug differs from chlorothiazide in that a trifluoromethyl group is substituted for the chloride atom.

2. Both short-term and long-term studies in a large group of patients with congestive heart-failure who previously had required at least a weekly mercurial diuretic injection proved flumethiazide to be a potent and safe diuretic agent. A maximal effect, manifested by weight loss, was obtained with a dosage of 1000 mg. twice daily. Increased dosage produced no further response.

3. Bio-assay studies showed that flumethiazide produces a marked natruretic effect. With a therapeutic dose of 200 to 2000 mg., the sodium excretion in response to flumethiazide was similar to that of chlorothiazide. Potassium excretion was much less than was sodium loss, especially with the higher dosages.

4. Renal function studies revealed no significant change in the glomerular filtration rate, renal plasma flow, or blood pressure during the period of observation.

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Self-help Devices:

Bathing Aids

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Institute of Physical Medicine and Rehabilitation
and the Arthritis Self-help Device Office*

New York University-Bellevue Medical Center, New York

FIGURE 1. Strategic placement of rails or grab bars helps the disabled patient to get into and out of a tub by himself. An authoritative booklet on the relation of rail and grab bar placement to body mechanics entitled "Reach for Safety" is published by and available from the National Steel Products Company, 424 North Mansfield, Los Angeles.

FIGURE 2. Patients who can step over the rim of the tub but need some support will find the Lifeguard Rail helpful. It is easily installed. Information on local sources is available from Bollen Products, 1366 Shoreview Avenue, East Cleveland 12. Cost of unit is about $20.00.

FIGURE 3. Height of the tub can be reduced by use of stepping stools that are sturdy and covered with rubber treading to prevent slipping.

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*Supported at the Institute by the Arthritis and Rheumatism Foundation.

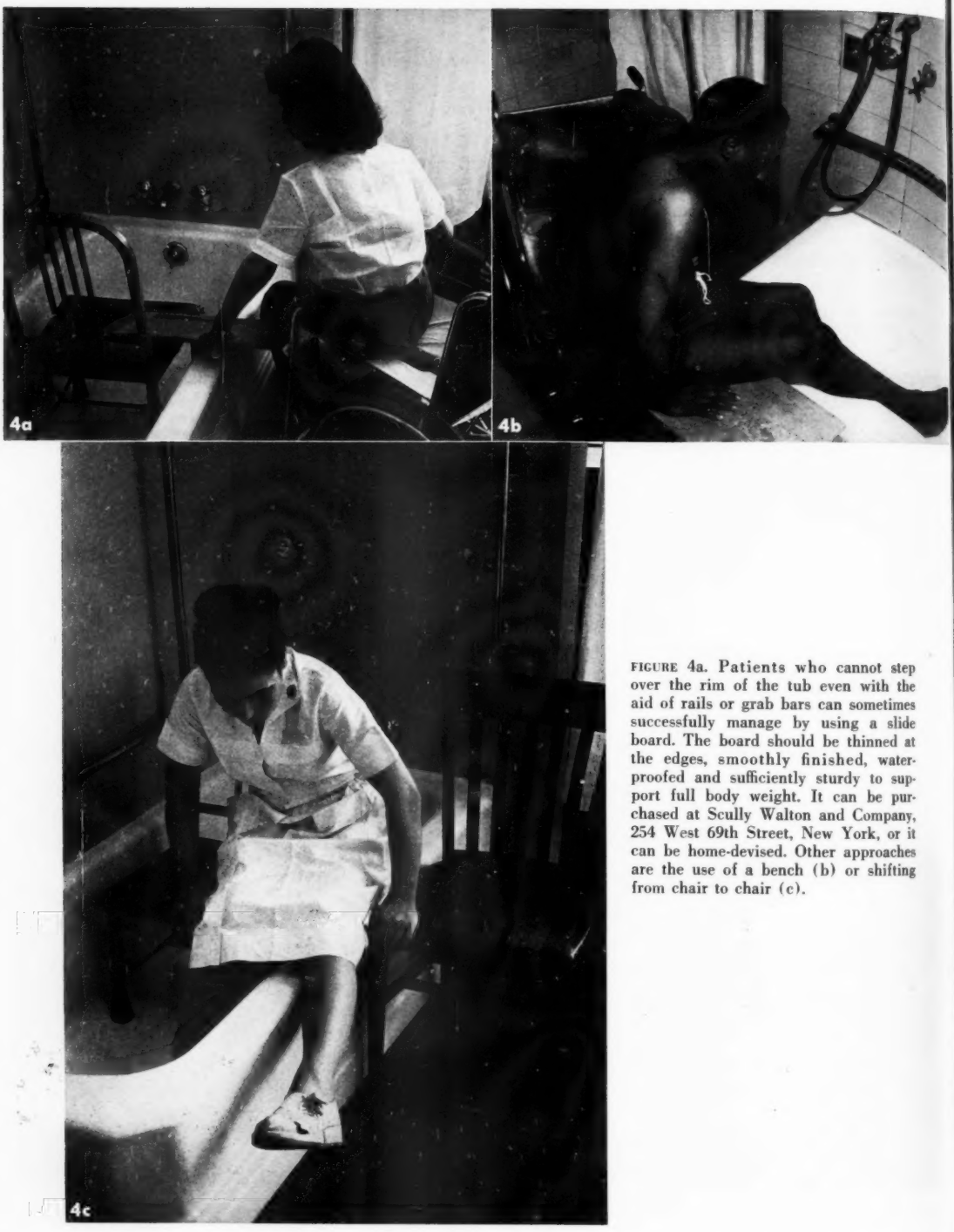

FIGURE 4a. Patients who cannot step over the rim of the tub even with the aid of rails or grab bars can sometimes successfully manage by using a slide board. The board should be thinned at the edges, smoothly finished, waterproofed and sufficiently sturdy to support full body weight. It can be purchased at Scully Walton and Company, 254 West 69th Street, New York, or it can be home-devised. Other approaches are the use of a bench (b) or shifting from chair to chair (c).

FIGURE 5a. The patient who is unable to lower himself to the bottom of the tub may be able to bathe satisfactorily sitting on a stool, bench or chair in the tub and using the Ever-Ready Shower Hose. The hose may be attached to the wall by suction at any height.

b. The Adjusto is a new plumbing device which provides a standing or sitting shower or a tub filler in a single unit. Several conversion units are available to fit most tub fixtures. The Queen Mary shown here costs about $25.00. A catalogue may be obtained from Milwaukee Faucets, Inc., 301 East Reservoir Avenue, Milwaukee 12.

5a

FIGURE 6. The Dalton Bath Chair Lift may be helpful to the patient who cannot step into the tub, but who has sufficient strength in the upper extremities to manipulate a pump which will lower him to the floor of the tub. The Dalton Company, Rivera, California, also sells a motorized unit which can be completely controlled by the bather who is able to exert minimal pressure on a rubber bulb.

FIGURE 7. For the very severely disabled patient who must be carried to the bathtub and then lifted into it, a lifter may be the answer. Most lifters are manually operated by a hydraulic pump which elevates and a release mechanism which lowers. Motorized units are available.

Aside from the cost and the space needed, the choice of one lifter over another is contingent on many individual factors. A copy of *Device News* which contains information on lifters and lists manufacturers may be obtained from the Arthritis Self-help Device Office, 400 East 34th Street, New York 16.

5b

FIGURE 8. A nonskid mat should be used in the tub at all times. A wet bath towel will serve the same purpose. The suction-type Rubber Maid Mat shown here is one of the most secure. Price ranges from $2.00 to $4.00.

Readers are invited to submit suggestions and ideas for devices they have developed or know about and would like to share with others. Forward all such comments and suggestions to: Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

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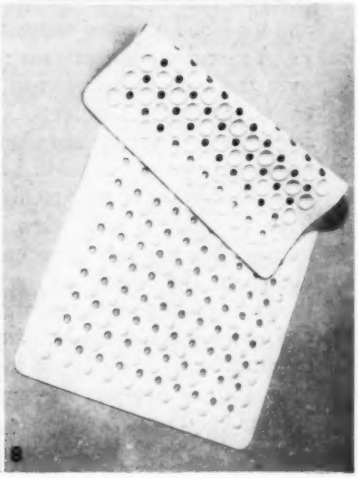
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CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Gillesby, M.D., Assistant Chief, Surgical Service

Case Report

DR. STANLEY E. LAWTON (attending surgeon): A 60 year old carpenter was admitted to Hines Veterans Administration Hospital complaining of chills, fever, anorexia and malaise of one week's duration. During this time, he had noted clay-colored stools and dark-colored urine, and had vomited once. His friends had told him that he looked a "little yellow" for a week prior to the onset of his symptoms. The history further states that he had not received any blood transfusions, injections or medications. He had been a "heavy drinker" for approximately 30 years.

At admission, his temperature was 99.6° F., and his blood pressure was within normal limits. A macular erythematous rash was present over the back and abdomen, with some excoriations on the shoulders. The sclerae were icteric and the lungs were clear. The heart was of normal size and a grade 1 systolic murmur was heard at the apex. An enlarged, nontender liver, palpable 5 cm. below the right costal margin, was the only abnormal finding in the abdomen. The contour of the liver's edge and the gallbladder were not mentioned. The spleen and kidneys could not be palpated. On rectal examination, a few external hemorrhoids were seen, and the prostate was nontender, slightly enlarged and firm.

The red blood cell count was 3,500,000, and the white blood cell count 11,800. A differential count showed 75 polymorphonuclear cells, 24 lymphocytes and 1 eosinophil. The hemoglobin was 11 gm. and the hematocrit 33. The urine contained large amounts of bile, but no sugar or albumin. Nonprotein nitrogen was 29, alkaline phosphatase 35, and the albumin-globulin ratio 3.1 to 4.3. The direct van den Bergh reaction was 22, and the indirect 11. Amylase readings were 35 and 44. All of these tests were repeated several times with little change in results, except for a gradual increase in the amount of bile found in the blood and urine. Stools were clay-colored, but I fail to find a report on the presence or absence of occult blood. Blood in the stool, which may occur in ampullar or ductal malignancies, often serves as a valuable aid in differentiating these conditions from tumors arising in the pancreas.

At this point, it seems timely to ask for a report on the roentgenograms made of the chest and the gastrointestinal tract. The protocol states that "the right hemidiaphragm is polyarcuate, and the left normal. There is a suggestion of extrinsic pressure on the first portion of the duodenum, which could be due to an enlarged gallbladder or liver. The duodenal loop is within normal limits."

DR. WILLIAM E. FREDERICK (assistant chief, radiology service): The fact that a diaphragm

is polyarcuate does not really mean much as far as the case itself is concerned.

Roentgenographic examination of the chest showed only slight pulmonary emphysema and some calcium in the aortic arch. The gallbladder was not visualized. Films of the gastrointestinal tract showed an enlarged papilla. The defect was confirmed in a view of the papillary portion and the distal area of the first segment of the duodenum. We would conclude from this that the patient had a defect compatible with pancreatic disease—either inflammatory or neoplastic.

DR. LAWTON: Four days after admission, the patient had some tenderness in the right upper quadrant and the epigastrium. Again no mention was made of the gallbladder or any palpable irregularities along the margin of the enlarged liver. Jaundice became more acute while further tests were being made.

To digress a moment from the protocol, the pathologic causes and mechanism of jaundice have long been subjects of controversy. Obstructive jaundice mechanically produced by stones, strictures and tumors is comparatively easy to understand, but jaundice in patients with cirrhosis, viral or toxic hepatitis, or fatty liver due to alcoholism is not simply explained. In this case, a month was spent in study and administration of medical treatment before the decision was made to operate.

At laparotomy the findings were as follows: "When the peritoneal cavity was explored, a firm mass was palpated in the region of the head of the pancreas. The liver was enlarged. The gallbladder was greatly distended and contained about 400 cc. of black bile." The surgeon was confronted here with one of the most difficult situations in surgery—a mass of undetermined origin in the head of the pancreas. If the mass was malignant, Whipple's operation was to be considered; but, if it was inflammatory, this most certainly should not be done. Mistakes have occurred so frequently in the diagnosis of pancreatic neoplasms that many surgeons rarely do radical operations, and some surgeons have abandoned them. Uncertain about the diagnosis and being forced to make a decision, the surgeon in this case removed tissue from the liver and pancreas for microscopic examination. A cholecystogastrostomy was performed to decompress the biliary tract, and the abdomen was closed. Whether the biopsies were by excision or needle was not stated. Regardless of the method used, I am sure the surgeon removed the tissue with considerable misgiving. It has been learned by bitter experience that the removal of pancreatic tissue under these conditions is not without danger. Satisfactory biopsies are difficult to obtain, may be misleading, and frequently cause serious complications.

May we now have the results of the biopsies.

DR. MYRON E. RUBINTZ (chief of laboratory service): A photomicrograph of the specimen taken from the head of the pancreas at the time of the operation showed the architecture of the pancreas to be somewhat distorted. It was apparent that the lesion was inflammatory. An islet, an infiltrate of inflammatory cells and some fibroblasts or fibrosis, and a very hazy appearance of the acinar arrangement of the glands and ducts were seen. These findings seemed to indicate some type of chronic pancreatitis; at least, that was all there was in the specimen that we received.

A section from the liver showed probable biliary cirrhosis or, at least, an obstructive type of lesion of the liver, with a large amount of retained bile in both the cells and the sinusoids. There was no evidence of tumor.

Both biopsies showed chronic pancreatitis and, as you would expect from the icterus, an obstructive type of biliary cirrhosis or, at least, some obstruction to the flow of bile in the liver.

DR. LAWTON: Surgery was completed without complications, and the patient withstood the operation very well. On the following day, he became dyspneic for a time, and on the second day he was somewhat confused. A copious amount of bile flowed through a Penrose drain which projected through a stab incision in the right lower quadrant of the abdominal wall. On the sixth postoperative day, the drain was removed. Subsequently the patient's temperature began to rise, and two days later it was 104° F. Blood pressure dropped to 98/60, and he was maintained on LEVOPHED® bitartrate. Bowel sounds were absent. Of interest are the leukocyte counts of 57,000 four days before

death and 52,000 on the day of death. During this period, the patient was afebrile. He died on the fifteenth postoperative day.

Much can be learned from this case. An attempt to predict autopsy findings brings up two most important questions: (1) Was there a malignant tumor present which was missed in the biopsies? (2) Did the removal of tissue for diagnosis initiate an acute pancreatitis which resulted in fatal complications? *Chronic pancreatitis* as a primary diagnosis has already been established from the microscopic sections. In presenting his diagnosis, I noticed that the pathologist added a protective clause: "at least, that was all there was in the specimen that we received." Consequently, I am venturing the additional diagnosis of *carcinoma of the head of the pancreas.* Ordinarily, chronic pancreatitis alone would produce more pain and less jaundice than this patient had. On the basis of history and biopsy findings, one would expect to find alcoholic and obstructive types of cirrhosis of the liver. From the copious amount of bile drainage reported, one must conclude that a bile peritonitis had developed. The possibility of a leak at the site of the anastomosis cannot be overlooked. An acute pancreatitis must have been present with fat necrosis and thrombo-embolism, which are seen frequently in this type of pancreatic disease. I am at a loss to explain the extremely high leukocyte count of 57,000 in an afebrile patient whose differential count offers no clues. An infection must have been present somewhere, unless the hematologists have a more plausible explanation.

Findings at Autopsy

At autopsy there was extreme jaundice and a very marked peritonitis with approximately 600 cc. of bile-stained ascitic fluid and 200 cc. of bile-stained fluid in the pleural cavities. A necrotic mass in the gastrocolic ligament appeared to be fat necrosis rather than a type of neoplasm. The liver was enlarged, weighing 2000 gm., and was smooth and dark green in appearance. Although the patient had a long history of alcoholism, he did not have any apparent gross alcoholic or dietary cirrhosis. The hepatic biliary system seemed dilated and the hepatic vessels, the portal veins, were all patent. The extrahepatic biliary tree appeared essentially normal. The pancreas, which seemed to be the point of contention in this case, showed a somewhat distorted architecture, but no neoplastic lesion was found.

On gross examination of the areas about the pancreas, fat necrosis similar to that seen in the gastrocolic ligament was apparent. The anastomosis seemed to have been healing well and there was no evidence of leakage. The area about the ampulla of Vater revealed some induration, but again there was no evidence of neoplasm. The kidneys were slightly enlarged, and from the amount of jaundice present it was not surprising to find the typical gross appearance of a bile nephrosis. A section from the area about the pancreas and in the region of the gastrocolic ligament revealed a hazy, cloudy, fatty substance, which is the saponification seen in fat necrosis. As is characteristic in these cases, evidence of calcification in the region of the fat necrosis indicates that the pathologic condition was obviously of long duration—that it was not only acute but also subacute and chronic. A few sections through the pancreas revealed almost the whole story: A very marked fibrosis, both perilobular and intralobular, had been destroying the pancreatic tissue. There was no evidence of neoplasm. A section through the area around the ampulla showed fibrosis, inflammatory cell infiltrate, and some obliteration and destruction of the duct structures; but again there was uniformity of the cells.

The diagnosis was chronic relapsing pancreatitis and acute hemorrhagic pancreatitis with bile peritonitis.

Differential Diagnosis and Discussion

DR. WILLIAM J. GILLESBY (assistant chief of surgical service): Our problem here in defining the difference between chronic relapsing pancreatitis and carcinoma of the pancreas has not changed one particle in 50 years, and this case was a sacrifice on the altar of attempting to determine this difference. As you may have noticed, this case occurred about three and one-half years ago, when we were doing transduodenal pancreatic biopsy with a

Silvermann needle. We did about 13 and obtained very fine specimens. This patient was the first to die as a result of this method of biopsy. Another death occurred later, so we abandoned the procedure. Some articles state that needle biopsy is a safe procedure. *It is not.* In order to cure a carcinoma of the pancreas, you must first recognize it. That is our problem, and we have not yet found a solution for obtaining a biopsy without risk.

What happens when a needle is inserted into the pancreas? Trypsinogen in the pancreas is inactive until it is activated by enterokinase. I think that the trypsinogen, although not in contact with the intestinal fluid, finds enough enterokinase in the blood and the hemorrhage that occurs as a result of the biopsy to change it into trypsin, and acute hemorrhagic pancreatitis ensues. Incidentally, W. J. Mayo said many, many years ago that 15 per cent of the patients with carcinoma of the head of the pancreas in whom he had done a cholecystogastrostomy or cholecystoduodenostomy were alive at the end of 15 years. The diagnosis must have been in error.

I think that it has been clearly shown in the case under discussion that a differentiation between malignant and chronic relapsing disease of the pancreas cannot be made by palpation.

If the pancreas is obstructed—and this pancreas was definitely obstructed—I believe needle biopsy is even more of a risk, because fluid cannot drain into the duct and the pancreatic juice effuses into the tissue, hemorrhage occurs, acute hemorrhagic pancreatitis ensues, and the patient dies! As Dr. Lawton pointed out, the number of patients who have been sacrificed in an attempt to save them by using the Whipple procedure is quite a serious matter, because we have lost entirely too many and saved too few in the effort. We are quite modest about our results in carcinoma of the pancreas, and in the language of Sir Winston Churchill, "Mind you, we have got a great deal to be modest about."

DR. ARMAND LITTMAN (chief of medical service): This case is a remarkable one in that it combines two entities, each of which is extremely uncommon, in a disease that is uncommon. The first is the syndrome of painless pancreatitis. We all recognize it from time to time; for example, it comes up in the differential diagnosis of diabetes. Nowhere in this protocol are we told that the patient had much pain, and certainly not the kind of pain that would lead us to suspect that there was a chronic benign process. Although we think of painless pancreatitis in cases of sialorrhea pancreatica and diabetes, or, in other words, in the presence of mesenchymal failure of the gland, we seldom consider it in cases of mechanical or obstructive lesions.

The second entity is jaundice. The only series that I know of in which there was jaundice in relapsing pancreatitis, at least in the American literature, are the seven cases reported by Sydney Selesnick at the Veterans Administration Hospital operated by the Yale University School of Medicine at New Haven, and I do not think that even Dr. Selesnick had a case in which there were both jaundice and painless pancreatitis. This is quite an unusual combination.

I would like to point out that the crude technics of biopsy with a needle are not appropriate to the pancreas, and I think that Dr. Gillesby has done a splendid job in giving the reasons why they are not. There is no way of obtaining pancreatic tissue without violently interrupting the continuity of the organ's function. Tissue may be removed from the liver and kidney without causing much trouble; however, these viscera are not dangerous in the same way that the pancreas is. In the pancreas, a very minor trauma may set up a chain reaction that will persist until the patient dies. Fortunately, a better method of coping with this vicious property of the pancreas, and one that should be employed more often, is the use of biliary drainage and the secretin test.

H. F. Raskin of the University of Chicago School of Medicine, who has had a great deal of experience with intubation technics, has discovered a way to put a tube down into the duodenum in 15 to 20 minutes without using a fluoroscope. In the half-dozen or so cases in which I have used this procedure and the dozen or two in which residents working with me have used it, we have not had any mishaps, and we have not worked with the tube more

than 15 or 20 minutes. Raskin's method when strictly followed is almost foolproof.

Utilizing this intubation technic, we have employed the secretin test in cases of jaundice to determine the type and site of lesion present. If the patient has obstruction in the extrahepatic biliary tree, the intravenous administration of a dose of secretin may produce a brisk flow of pancreatic juice—if it is not obstructed by the tumor—with a normal volume of bicarbonate concentration, which is actually all that needs to be measured. On the other hand, if the patient has a lesion which completely obstructs the common duct area, as was true in this case, nothing will come from the tube.

In the case of possible pancreatic carcinoma, suspected on the basis of systemic manifestations, metastatic nodules, attacks of pain, or something other than jaundice, a further contribution of Raskin's will be of assistance. He has found that stains made on the washout from the pancreas collected during the last 15 or 20 minutes—perhaps 20 or 30 minutes after administration of the secretin—were positive for carcinoma of the pancreas in 90 per cent of cases in which the lesion was proved to be present. I know of two cases that he reported positive in which the surgeon at laparotomy could not find the carcinoma. In both instances, under a little bit of duress, the surgeon did pancreatectomies and the tissue revealed neoplastic lesions.

DR. GILLESBY: Chronic relapsing pancreatitis chokes off the common duct at its point of entry into the region of the pancreas, causing it to become a fine tract that can hardly be seen. The pancreatic ducts are also dilated, resulting in obstruction in both the biliary tree and the pancreatic system. Warren H. Cole has reported on six cases in which chronic relapsing pancreatitis choked off the duct in the substance of the head of the pancreas. I think we are beginning to see this quite frequently; it also has occurred in three of our cases of pseudocyst of the pancreas.

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1959 NOBEL PRIZE WINNERS IN MEDICINE

Two American investigators, Drs. Severo Ochoa of the New York University College of Medicine and Arthur Kornberg of the Stanford University School of Medicine, were the winners of the Nobel prize in medicine and physiology in 1959. Drs. Ochoa and Kornberg are biochemists, which indicates perhaps the great extent to which biochemistry now dominates medical investigation.

Dr. Ochoa was born in Spain, graduated from the University of Madrid in 1929, and did postgraduate work in Glasgow, Berlin, Heidelberg and London. He came to the United States in 1941 to become instructor and research associate in pharmacology at Washington University, St. Louis. He then moved in 1942 to New York University College of Medicine, where he became chairman of the department of biochemistry in 1954. Now a United States citizen, he has previously received other recognition for his contributions in his chosen field.

Dr. Kornberg also was at one time at Washington University, St. Louis, where he became head of the department of microbiology. He was born in Brooklyn, March 3, 1918, graduated from City College in 1937, and received his M.D. degree from the University of Rochester School of Medicine and Dentistry in 1941. His wife is also a biochemist. For 10 years, from 1942 to 1951, Dr. Kornberg was with the United States Public Health Service as a staff member of the National Institutes of Health, Bethesda. In 1947 he was a guest researcher in the department of pharmacology and chemistry at New York University College of Medicine and there he collaborated with Dr. Ochoa.

In their award the Nobel prize winners are cited for discoveries related to the biologic synthesis of ribonucleic acid and deoxyribonucleic acid, commonly called RNA and DNA, respectively. DNA is considered to be the chemical substance that carries hereditary qualities from one generation to the next. RNA is involved in the production of protein and is considered to be the substance which

may establish the nature of viruses. Dr. Ochoa found an enzyme capable of promoting production of RNA from organic substances available commercially. He found this enzyme in the intestinal variety of *Escherichia coli*, bacteria which turn alcohol into vinegar. Dr. Kornberg discovered an enzyme that promotes production of DNA from smaller organic molecules.

In its statement, the Nobel Prize Institute concluded that these biochemists have not solved the question "What is the origin of life?" but "they clarified many of the problems of regeneration and continuity of life."

These contributions in the field of basic science will undoubtedly play a part in the further development of knowledge concerning life itself. Conceivably, the basic scientists are unraveling the mechanisms of living processes. Such research as this may be the foundation for investigations that will enable medical science to prevent the birth of children with congenital malformations. The nucleic acids have become recognized as the substances which play a major role in the origin of life and as the factors involved in the transmission of heredity and in the continuous evolution and changes seen in viruses, bacteria, animals, men and indeed all living things. In the processes of life, infinite varieties of living bodies appear because of the rearrangement of the DNA molecules. DNA is the major constituent of the genes.

The choice by the Nobel Prize Commission of its 1959 winners indicates that the method by which the Commission chooses its recipients, at least in the sciences, is itself an excellent scientific technic.

MORRIS FISHBEIN

VERTIGO

In his presidential address for the Section of Otology of the Royal Society of Medicine, London, Dr. Terence Cawthorne[1] noted that the underlying cause of dizziness is often found in a disordered vestibular system. Hence, the otologist is sought for help when vertigo is the main complaint. Anything from a head injury to too much streptomycin may cause vertigo by disturbing the vestibular labyrinth. Nausea and vomiting, which are part of the vagal effect which often accompanies a severe vestibular disorder, may be so severe as to overshadow the vertigo. Dr. Cawthorne defined vertigo as "any hallucination of movement, no matter what its character." The senses of the patient are deceived either into seeing, the objects around him in motion or into feeling that his head or sometimes his whole body is moving when, in fact, movement is not taking place.

The frequency of the symptom was determined by investigating its incidence among 106 general practices serving almost 400,000 people. The study showed that vertigo as a symptom which caused people to consult the doctor was of the same frequency as peptic ulcer, pneumonia or rheumatoid arthritis.

The symptoms associated with vertigo related to the digestive tract often lead to the belief that some food to which the person is sensitive may be responsible. Obviously, the effects on the labyrinth have been brought about by some disturbance of its blood supply. Many people believe that the eyes are primarily responsible, yet Dr. Cawthorne stated that he has never seen a case of vertigo which could be attributed to an ocular disorder. The transient dizziness on suddenly getting up or changing posture or following a hot bath is more related to cardiovascular instability than to a vestibular disorder. Indeed, Dr. Cawthorne also noted that the hot flashes accompanied by a feeling of fullness in the head, which the patient may describe as dizziness and which are part of the menopause, have resulted in attempts to relate the menopause and vertigo. Finally, there is, of course, the group who would assign a psychosomatic cause to vertigo. In considering this theory, Dr. Cawthorne stated that vertigo itself can engender a feeling of insecurity in the most stouthearted of sufferers.

Causes within the central nervous system are necessarily serious to health and to life. The first duty of the physician when confronted by a patient with vertigo is to exclude the possibility of a disorder within the central nervous system. If this can be done, the cause

may be sought in the internal ear. Finally come the effects of circulating toxins. Today the main cause under this heading is streptomycin, although, from time to time, alcohol and tobacco have been said to play major roles. The proof that they are not of major significance is the fact that abstinence from either tobacco or alcohol seldom helps permanently any case of vertigo. Obviously, the distinction between vertigo related to the internal ear and that associated with epilepsy, disseminated sclerosis, thrombosis of intracranial blood vessels, or tumors is a problem for the specialist in neurology.

Meniere's disease accounts for more than twice as many instances of vertigo than does any other disorder. Prosper Meniere of Paris was the first to call attention to the ear in its relationship to vertigo and vomiting associated with tinnitus and deafness. This discovery was made in 1861. In 1938, Hallpike and Cairns demonstrated that Meniere's disease was accompanied by a distention of the endolymphatic system. The condition also has been called endolymphatic hydrops. The principal features of this disorder are as follows: (1) It is usually unilateral. (2) The attacks are sudden and of limited duration. (3) Balance and hearing are usually affected. (4) Hearing is often distorted. (5) Hearing and noises often fluctuate with the attacks. The attacks come on suddenly and rarely last more than two hours.

Other causes of vertigo, such as perilabyrinthitis and vestibular neuronitis, also may require special study. Infection may spread from the middle ear to the bony labyrinth; with this condition dizziness frequently occurs.

Especially interesting to the general practitioner is the vertigo caused by the specific toxic properties of streptomycin in various forms. Dihydrostreptomycin unfortunately has a toxic affinity for hearing as well as for balance. Some patients apparently have been so susceptible that vestibular function has been severely damaged with the administration of as little as 3 gm. of streptomycin over three days. This is especially true when there is also impairment of renal function. Frequently, the early symptoms of streptomycin intoxication have been credited to the fact that the patient who is in bed complains of having the "swimming feeling" when being turned, so that the symptom is credited to the illness rather than to the drug. Cawthorne is convinced that many patients can tolerate 1 gm. or even 1.5 gm. of streptomycin a day for several weeks without having toxic symptoms, but he believes that the dosage of 0.5 gm. daily should never be exceeded, as toxic symptoms have never been recorded with this dosage.

MORRIS FISHBEIN

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1. Cawthorne, T.: Vertigo. Proc. Roy. Soc. Med. 52:529-536 (July) 1959.

NEW AVERAGE WEIGHTS

The largest statistical evaluation of body build and blood pressure ever published has just been released by the Society of Actuaries. As a result the tables of average weights which appear in textbooks, guides to public health, and on the scales in doctors' offices will have to be changed, since the new average weights differ remarkably from those which were published 30 years ago. The weights of women from 20 to 30 years old average at least 5 lb. less than they did then. Women of all ages are now, on an average, lighter than they were in the previous era. The vogue for slenderness has outmoded the enjoyment of contours such as those that were displayed by Lillian Russell.

The average weights of men of short and medium height in the age group 20 through 40 are now about 5 lb. more than they were formerly. The proportion of men who are underweight has diminished, while the proportion of underweight women has increased appreciably.

As has long been recognized, the weights of both men and women increase with advance in age through the 50s. Men begin putting on weight in the 20s and level off in the 40s. Women stay slim until the 30s and usually do not start putting on weight until after the middle 30s. The actuaries for the insurance companies found that men who weigh 20 lb. above the average incur a penalty of about 10 per

cent higher mortality. Those weighing 25 lb. above the average are subject to a 25 per cent higher mortality, while weights 50 lb. above average are associated with an excess mortality up to 50 per cent or even 75 per cent. This permits the slogan that every pound of weight above the average adds another 1 per cent in increased mortality. Women are able to stand added weight better than are men, as shown by the increased life expectancy for women. The penalty of increased weight shows itself particularly in the increased mortality in diabetes and in digestive disorders, such as gallbladder disease, which come with increased weight.

As proof that weight reduction pays, the insurance actuaries state that "Those who were overweight when insured, but were later given standard insurance because of sustained weight reduction, showed an immediate benefit of normal mortality, which continued for at least 10 years. After that, some of them apparently relapsed and put on weight again." The mortality for the group as a whole then began to increase.

Systolic blood pressures above 150 mm. of mercury or diastolic blood pressures above 100 mm. are associated with an excess mortality of 75 to 125 per cent. Apparently, women withstand high blood pressure much better than do men. The lowest mortality rates of both men and women are found in people with blood pressures that are below the average.

In addition to establishing the relationship between elevated blood pressure and mortality, the insurance actuaries found that persons who have high blood pressure and are overweight in combination with albuminuria, persons whose family history shows two or more cases of early cardiovascular renal disease, and persons who are overweight in combination with an elevated blood pressure have serious increases in mortality.

The kind of study here reported could be made only by an agency such as the Society of Actuaries, which is a professional organization that includes principally the actuaries of life insurance companies. Some 2000 actuaries hold membership. The chairman of the Society's committee which made this study is Edward A. Lew, actuary and statistician for the Metropolitan Life Insurance Company. The life insurance companies which participated in this study represent more than two-thirds of all the life insurance in force at this time.

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► COLOR ATLAS AND MANAGEMENT OF VASCULAR DISEASE

By William T. Foley, M.D., Associate Professor of Clinical Medicine, and Irving S. Wright, M.D., Professor of Clinical Medicine, Cornell University Medical College, New York. 183 pages with 194 illustrations. 1959, Appleton-Century-Crofts, Inc., New York. $18.00.

The excellent color photographs of the extremities as they appear in different peripheral vascular diseases make this atlas a valuable reference book. The principles of management outlined in the monograph are available in any of the several standard books on peripheral vascular disease; however, as the authors of the book state, the physical appearance of the extremities does play a significant role in establishing a diagnosis. One who sees many and various peripheral vascular diseases may not need a book such as this, but the physician who sees only an occasional patient with difficulties of the extremities will find the atlas very valuable.

The book is primarily a compilation of case histories illustrated by photographs and x-rays and including descriptions of the treatment and results obtained. The serial photographs dramatically show the effects of therapy far better than do descriptive comments.

Arterial and venous diseases, lymphedema, limb disorders with vasospasm as a factor, aneurysms, diseases of the small vessels, and blood vessel tumors are discussed. The surgical treatment indicated is only mentioned; no description of actual technic is given, nor is there a discussion of the merits of different operations. Statistical figures are kept at a minimum, since in some instances only a case or two is presented.

Y. S.

► THE YEAR BOOK OF CANCER (1958-1959)

Compiled and edited by Randolph Lee Clark, Jr., M.D., Director and Surgeon in Chief, and Russell W. Cumley, Ph.D., Director of Publications, University of Texas M. D. Anderson Hospital and Tumor Institute, Houston. 570 pages with 202 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $8.00.

Containing 298 abstracts selected from a total of 4000 articles, this text covers every aspect of cancer. Two-thirds of the articles are from American journals, the remainder having been chosen from foreign publications. The editorial board for the book consisted of 24 different groups, each representing a particular phase of the problem of cancer. Controversial material is omitted, but important reports on basic science and research in this field are included.

The bulk of the material is on tumors of the various regions of the body, presented according to regional anatomy and major systems. Sections not oriented to the clinical aspects of tumor are those on epidemiology, biochemistry, physics, bacteriology, immunology and virology. Animal tumors also are considered. Other discussions are on cancer in children, roentgenographic diagno-

(Continued on page A-170)

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1. Based on estimate by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122 (Jan.) 1933

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sis, chemotherapy and hormone therapy, reconstruction and rehabilitation, management of advanced tumors, and terminal care.

The area covered is broad, and the sampling of material is adequate to furnish the busy physician with a panorama of progress in cancer care. The illustrations, charts and graphs enrich the presentation of the abstracts. Short, appropriate comments inserted by the editors are also instructive. Nearly every abstract contains pertinent data in statistical form; hence, the material presented is not just a viewpoint, but a summary of actual experience.

Y. S.

► MOLECULES AND MENTAL HEALTH

Edited by Frederic A. Gibbs, M.D., Professor of Neurology, University of Illinois College of Medicine, Chicago. 189 pages with 52 illustrations. 1959, J. B. Lippincott Company, Philadelphia and Montreal. $4.75.

A collection of papers from the scientific conferences of the Brain Research Foundation, this book has an impressive list of contributors. It begins with a significant quotation by Dr. Gibbs: "We have probed the depths of space and scrutinized the interior of the atom, but we have hardly begun to explore the universe that lies between our ears."

This text is hardly meant for the beginner, as it deals with somewhat advanced theories and technical papers, but it will be of extreme pertinence to those concerned with the surge of interest in psychopharmacology.

The first part of the book, covering amines in relation to brain function and behavior, includes discussions of dramatic recent developments in the field of psychopharmacology, which many investigators feel is the key to the solution of mental illness. There is a chapter devoted to current work on ceruloplasmin in mental illness and also one on the effect of ceruloplasmin in a case of schizophrenia. The chemistry of substances such as acetylcholine, epinephrine and norepinephrine and tryptophan and their relationship to behavior are discussed in detail.

Part 2 of the book is a rather detailed discussion of hypsarrhythmia and the results obtained by treating this condition with ACTH.

E. M. L.

► AN ATLAS OF NORMAL RADIOGRAPHIC ANATOMY

By Isadore Meschan, M.D., Professor and Director, and R. M. F. Farrer-Meschan, M.D., Research Associate, Department of Radiology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina. Ed. 2. 759 pages with 412 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $16.00.

While the original purpose of this text has been maintained, it has been expanded and brought up to date. The book offers a modern compendium of morbid anatomy as it applies to roentgenography, the technic used in obtaining roentgenographs, the significance of the film obtained, the parts which can be visualized on these views, growth and development, and normal variants as seen in roentgenographs.

As one might anticipate, much of the original format has been maintained, because it still is as applicable today as it was when the first edition was published in 1951. Sections are separated according to the upper extremities, pelvis and lower extremities, the skull and its detail, the brain, vertebrae and arachnoid space, the respiratory system, mediastinum, heart and major vessels, the upper and lower alimentary tracts, the biliary tract, the abdomen and peritoneal space, the urinary tract, and the genital system.

In view of its new importance, a section on basic radiation protection has been added, and the section on growth and development of bone has been completely rewritten to comply with the new advances in the field. This of course means that more inclusive tables on growth of bone have been incorporated. Encephalography, cerebral angiography and myelography also are more adequately discussed in the new edition than in the former one.

Advances in basic knowledge of the physiology, anatomy and roentgenographic manifestations of the heart and great vessels are presented as in an introductory text. Advances in the technical means of demonstrating abnormalities as well as the normal anatomy of the gastrointestinal and biliary tracts also are described.

The basic plan of supplementing multiple pen-and-ink drawings with roentgenographic illustrations, which was used in the first edition, has been maintained.

S. B. F.

(Continued on page A-172)

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► MEDICAL MANAGEMENT OF THE MENOPAUSE

By Minnie B. Goldberg, M.D., Associate Clinical Professor of Medicine, University of California School of Medicine, Berkeley-San Francisco. Modern Medical Monographs. No. 17. 98 pages, illustrated. 1959, Grune & Stratton, Inc., New York and London. $4.50.

Written principally for gynecologists, this book clearly illustrates the various etiologic factors in the menopause. The author describes the various symptoms associated with the change of life and correlates the symptomatology as it is affected by the physiologic state.

The chapters on choice of therapy and management of the climacteric are well written. The author believes that successful therapy requires patience, perseverance and careful attention to minutiae.

E. A. B.

► ATLAS OF ROENTGENOGRAPHIC MEASUREMENT

By Lee B. Lusted, M.D., Associate Professor of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, New York, and Theodore E. Keat, M.D., Professor of Radiology, University of Missouri School of Medicine, Columbia. 176 pages with 119 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $9.00.

Prior to the discovery of the x-ray, knowledge of the normal internal anatomy of the human being was derived largely from the study of cadavers and, to some extent, from observations of operations. However, with the use of the roentgen ray, it has been possible to visualize the undisturbed internal anatomy of the living human in almost all parts of the body. A great deal of literature has accumulated on the measurement of anatomy, with detailed studies of the variations of the normal.

For the first time, much of this statistical data has been published in one volume. Reference to this book enables a comparison of the individual x-ray study with the known limits of the normal in such areas as the skull and central nervous system, the skeletal system, and the thoracic and abdominal organs.

This collection represents a compilation of known data on the subject roentgenographic measurement. It is not a presentation of new data, nor is it a critical study of the measurements of others. While the information given is, therefore, of varying value and significance, the book has the great virtue of bringing together for easy reference much of the known information.

R. G. L.

► PREVENTIVE MEDICINE

Edited by Herman E. Hilleboe, M.D., Commissioner of Health, and Granville W. Larimore, M.D., Deputy Commissioner of Health, State of New York, Department of Health, Albany, with 31 contributors. 731 pages with 59 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $12.00.

I agree with the editors that this book "sets forth a new way to look at preventive medicine for medical students, general practitioners, specialists and professional workers in official and voluntary health agencies." The main theme of the text is the distinction between the prevention of occurrence of disease and disability and the prevention of their progression.

Part 1 deals with preventing disease and disability and includes discussions of subjects such as potable waters, milk-borne illness, disposal of waste, food poisoning, and pollution of air.

The section on preventing progress of disease and disability evaluates periodic health inventories; screening for and detection of cancer: screening methods for pulmonary tuberculosis, heart disease, diabetes mellitus, and hearing and visual defects; and follow-up screening and diagnostic examinations.

The final section covers the supporting services for preventive medicine, including health education, education of the patient, communication, postgraduate education for physicians, social work, public health nursing, and the role of the hospital in preventive medicine.

This book has been prepared and edited with excellent understanding of the many problems of preventive medicine which face our population and almost all physicians. There is a great wealth of information in this volume, and I recommend it heartily.

I. P. F.

(Continued on page A-174)

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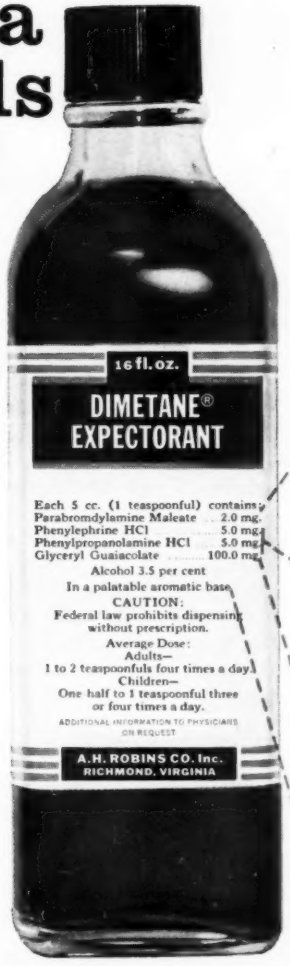
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► EARLY DIAGNOSIS

Edited by Henry Miller, M.D., Physician in Neurology, Royal Victoria Infirmary, Newcastle upon Tyne, England, with 25 contributors. 400 pages. 1959, The Williams & Wilkins Company, Baltimore. $6.50.

The discussions in this book stress findings and what to look for in various diseases. Among the many conditions considered are acute pain in the abdomen, acute specific fevers and alimentary tract and hypertensive vascular diseases. Each contribution is concise and to the point.

Throughout the book, emphasis is placed on "early diagnosis for early action for the cure, alleviation, and prevention of complications of a patient's illness, and for the protection of others."

I. P. F.

► SCHIZOPHRENIA
An Integrated Approach

Edited by Alfred Auerback, M.D., Assistant Clinical Professor of Psychiatry, University of California School of Medicine, Berkeley-San Francisco, with 15 contributors. 1959, The Ronald Press Company, New York. $5.50.

As stated in the preface to this book, "It is a paradox of modern psychiatry that the illness most commonly found in our mental hospitals is one about which there is still very little known." This book is not intended as a compendium on the vast subject of schizophrenia; rather, it is a collection of papers that were presented at the 1958 Hawaiian Divisional Meeting of the American Psychiatric Association.

Many students of the enigma of schizophrenia believe that it will be solved only by a multidisciplinary approach, which is the approach taken in this book. Recent studies in the neurophysiologic, biochemical and communicative aspects of schizophrenia are emphasized. Each chapter is written by an outstanding authority in a particular field of schizophrenia. Subject matter ranges from the basic attempt to define schizophrenia to discussions of the body image in the schizophrenic reaction, biochemical investigations in schizophrenia, neurophysiologic contributions to the understanding of schizophrenia, family relationships and cultural problems of schizophrenia, and the somatotherapy and psychotherapy of schizophrenia. The chapters are very well written and include a discussion of the material in each by another authority in the field. Each chapter also includes a fine bibliography.

Efforts such as this book will contribute to a better over-all understanding of schizophrenia and provide more or less of a common meeting ground for the various disciplines, so that information can be exchanged and expanded.

E. M. L.

► SURGICAL SERVICE GUIDE

By Louis T. Palumbo, M.D., Chief, Surgical Service, Veterans Administration Center, Des Moines. 208 pages with 22 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $6.00.

A rather brief guide to the policy and practice of the Surgical Service of the Veterans Administration Hospital in Des Moines, this small book probably will have only a limited appeal. However, it would be ideal for a person serving an internship or residency in surgery where a surgical service manual or procedure book is not available, as the material presented is rather typical of the policies of most surgical services in American hospitals.

The bulk of the book is on preoperative and postoperative orders for most of the common surgical procedures; however, the reasons for these recommendations are not discussed in detail. In addition to these rather specific instructions and precautions, the author has included information on the conduct of a surgeon, requisites of leadership, etc.

A number of illustrations demonstrate procedures such as methods of setting up tractions, making incisions, placing an ileostomy, arranging a catheter for chest drainage, and testing for arterial occlusion and incompetent leg veins.

The remaining portion of the book includes discussions of the management of complications such as adrenal insufficiency, diabetes, cardiac arrest, atelectasis and venous thrombosis, all of which are of utmost importance to a surgeon. Other sections are devoted to fluid management and diagnostic and follow-up procedures. Two short discussions on pediatrics and gynecology are also included.

Y. S.

(Continued on page A-176)

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► INTERNATIONAL TEXTBOOK OF ALLERGY

Edited by J. M. Jamar, M.D., Lecturer at the University of Louvain, Louvain, Belgium, with 31 contributors. 639 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $17.50.

In the preface to this book, the editor points out that "it has become extremely difficult, if not impossible, for one physician to write with sufficient competence on such varied phases as allergy of the respiratory tract, skin, eyes, digestive system, vascular and collagen tissue, as well as on the physiologic, immunologic and even botanic aspect, to discuss at the same time the morbid manifestations of the disease and the way to combat them, and introduce the reader to the many terra incognitae of Experimental Medicine."

Dr. Jamar solved these problems successfully by selecting men from all over the world to contribute to this volume. Each author has discussed the facet of allergy for which he is best qualified. The result is that each chapter represents an up-to-date, well-organized review of a particular topic.

To enumerate all of the problems considered would be superfluous, but the 25 chapters cover most of the many aspects of allergy. Although some chapters are not quite on the primer level, the book should be very helpful for the serious beginner.

Of particular interest are Rocha e Silva's chapter on anaphylaxis, Lawrence's review of the interrelationship of the various types of allergic reactions, Samter's recapitulation of the known and unknown aspects of asthma, Pearson's excellent discussion of treatment of status asthmaticus, Stokvis' introduction of the psychiatric methods used in allergic work to the neophyte, the very pertinent review of allergy in vascular and collagen diseases by Jiménez Diaz, and the discussion of allergy in hematology by Briggs and Verstraete.

Whereas the seasoned student realizes there are many honest differences of opinion in any field of medicine, flatly contradictory statements often are confusing to the beginner. The remarkable near-absence of internal disagreement in this book favors an uninterrupted formulation of concepts which can later be modified as conditions demand.

L. L. H.

► SURGERY OF THE FOOT

By Henri L. DuVries, M.D., Clinical Instructor in Surgery, Chicago Medical School, Chicago. 494 pages with 403 illustrations. 1959, The C. V. Mosby Company, St. Louis. $12.50.

Dr. DuVries wrote this volume in response to many requests for such a textbook. His original training was in chiropody, and he subsequently became a doctor of medicine. For nearly 30 years, he has devoted nearly all of his time and energy to the foot, and the reader of this text will be impressed with the many aspects of surgical treatment which he presents.

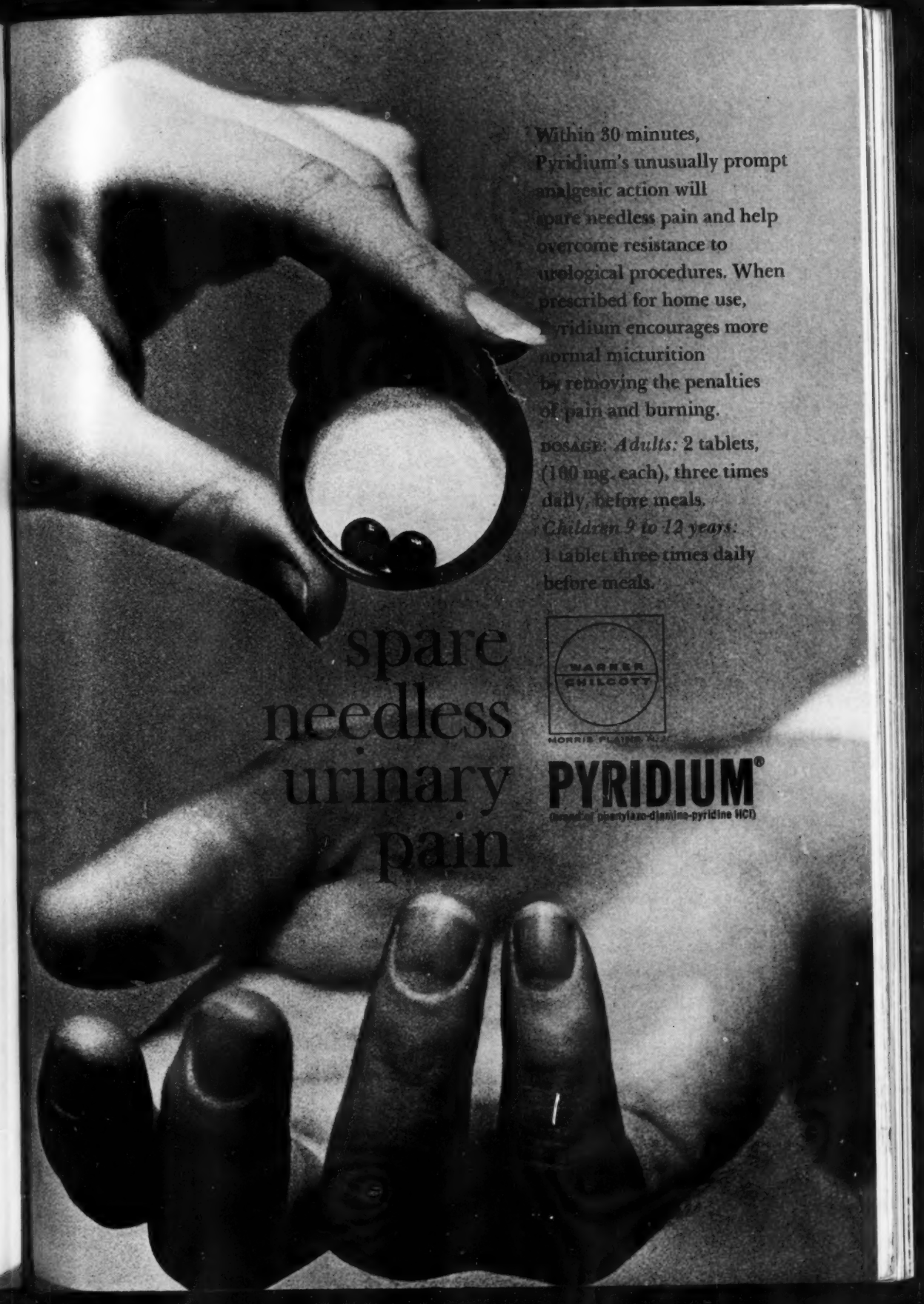
The book is especially interesting because emphasis is placed on some aspects of foot care which are not widely or extensively covered in the standard textbooks on orthopedic surgery and problems. This is particularly true of the well-written chapter devoted to diseases and deformities of the toenail. Numerous illustrations show the correction of some frequently seen deformities of the toenail which, for the most part, are glossed over quickly in standard textbooks on orthopedic surgery. The same may be said of a chapter devoted to the sesamoid bones and to their role in the production of foot symptoms. Clear and concise methods of treatment are suggested. The treatment of hallux valgus and other static deformities of the foot is well discussed; the author has recommended his own modification of the McBride procedure, which he used in treating 1200 cases of hallux valgus over a 25 year period. His results were excellent in 90 per cent of the cases.

In almost all instances, the discussion of surgical technics and procedures is well augmented by line drawings and by carefully annotated steps, which increase the teaching value of the text. The table of contents, index and illustrations are excellent, and, for the most part, the references are current and sufficiently extensive.

Surgical procedures for the correction of soft corns, overlapping fifth toe, sesamoiditis, and other commonly seen but not commonly discussed conditions are well covered in the text. Other textbooks on orthopedic surgery cover major deformities and operations on the foot as successfully as does this one, but this is the first text in which the minor yet important disabilities of the foot and their correction are emphasized.

E. W. J.

(Continued on page A-178)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► SYNOPSIS OF GYNECOLOGY

By Robert J. Crossen, M.D., Associate Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, St. Louis, Daniel W. Beacham, M.D., Assistant Professor of Clinical Obstetrics and Gynecology, and Woodard D. Beacham, M.D., Professor of Clinical Obstetrics and Gynecology, Tulane University School of Medicine, New Orleans. Ed. 5. 340 pages with 106 illustrations. 1959, The C. V. Mosby Company, St. Louis. $6.50.

In preparing the latest edition of this pocket-sized text, Dr. Crossen enlisted the help of Drs. Daniel and Woodard Beacham. Their complete revision of 12 chapters and the addition of material on endometriosis and complications of pregnancy have enhanced the value of this synopsis. In a most succinct and terse manner, this book supplements standard texts on gynecology and will serve as a quick reminder in differential diagnosis.

E. A. B.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.

Medical Discoveries: Who and When. By J. E. Schmidt, M.D., Chairman, National Association on Standard Medical Vocabulary. 555 pages. 1959, Charles C Thomas, Springfield, Illinois. $14.75.

Current Medical References. Edited by Paul J. Sanazaro, M.D., Associate Professor of Medicine, University of California School of Medicine, Berkeley-San Francisco. 535 pages. 1959, Lange Medical Publications, Los Altos, California. $3.50.

British Medical Bulletin. Current Virus Research. Symposium prepared by 18 contributors. Vol. 15. No. 3. 250 pages with 8 plates. 1959, Medical Department, The British Council, London. $3.25.

Acute Cardiac Pulmonary Edema. By Sigmund Wassermann, M.D., formerly associated with the First Medical Clinic, Vienna, Austria. 123 pages. 1959, Charles C Thomas, Springfield, Illinois. $4.25.

Pain and Itch; Nervous Mechanisms. Ciba Foundation Study Group. Edited by G. E. W. Wolstenholme, O.B.E. and Maeve O'Connor, B.A. No. 1. 120 pages with 41 illustrations. 1959, Little, Brown & Company, Boston. $2.50.

Handbook of Poisoning: Diagnosis and Treatment. By Robert H. Dreisbach, M.D., Professor of Pharmacology, Stanford University School of Medicine, Stanford-San Francisco. Ed. 2. 467 pages, illustrated. 1959, Lange Medical Publications, Los Altos, California. $3.50.

Chemistry of Pancreatic Diseases. American Lecture Series. By Harris Busch, M.D., Associate Professor of Pharmacology, University of Illinois College of Medicine, Chicago. 160 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $5.25.

A Manual for Histologic Technicians. By Ann Preece, H.T., Chief Technologist, Pathology Laboratory, Massachusetts Memorial Hospitals, Boston. 219 pages, illustrated. 1959, Little, Brown & Company, Boston. $6.00.

Upper Digestive Tract. The Ciba Collection of Medical Illustrations. Prepared by Frank H. Netter, M.D., with 9 contributors. Vol. 3. Part 1. 1959, Ciba Pharmaceutical Products, Inc., Summit, New Jersey. $12.50.

Lectures on the Interpretation of Pain in Orthopedic Practice. By Arthur Steindler, M.D., Professor Emeritus of Orthopedic Surgery, State University of Iowa College of Medicine, Iowa City. 733 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $18.50.

The Functions of the Endocrine Glands. By Peter F. Hall, M.D., Assistant Physician, Sydney Hospital, Sydney, Australia. 290 pages with 77 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $5.75.

Steric Course of Microbiological Reactions. Ciba Foundation Study Group. Edited by G. E. W. Wolstenholme, O.B.E. and Cecilia M. O'Connor, B.Sc. No. 2. 115 pages with 37 illustrations. 1959, Little, Brown & Company, Boston. $2.50.

X-ray and Radium in Dermatology. American Lecture Series. By Bernard A. Wansker, M.D., formerly, Instructor in Dermatology, Duke University School of Medicine, Durham, North Carolina. 114 pages with 20 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $5.00.

Progress in Hematology. Edited by Leandro M. Tocantins, M.D., Professor of Clinical and Experimental Medicine, Jefferson Medical College of Philadelphia, with 19 contributors. Vol. 2. 290 pages, illustrated. 1959, Grune & Stratton, Inc., New York and London. $9.75.

Diagnosis of Congenital Heart Disease. By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe and Bengt Jonsson. Ed. 2. 866 pages with 727 illustrations. 1959, The Year Book Publishers, Inc., Chicago. $28.00.

Neurological Complications of Lymphomas and Leukemias. American Lecture Series. By Henry M. Williams, M.D., formerly Special Fellow in Medical Neoplasia; Henry D. Diamond, M.D., Associate Attending Physician; Lloyd F. Craver, M.D., Attending Physician and Chief, Medical Neoplasia Service, Department of Medicine, and Herbert Parsons, M.D., Associate Neurosurgeon, Memorial Center for Cancer and Allied Diseases, New York. 134 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $5.75.

Clinical Auscultation of the Heart. By Samuel A. Levine, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, Boston, and W. Proctor Harvey, M.D., Associate Professor of Medicine, Georgetown University School of Medicine, Washington, D. C. Ed. 2. 657 pages with 660 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $11.00.

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A Periodic Review Of Your Investments - is sound practice, but it has particular value around year-end. An investment which appeared very promising at the time of purchase may have lost value due to intervening changes. In order to prevent further loss, it may be necessary to sell such investment. To the extent a tax deduction is allowed, taxes underwrite the real loss on investment.

Early in a year, you will not know what security transactions you will have during the year. However, in December, you are in a position to survey capital gains and losses realized earlier, decide whether it's to your advantage to make additional sales before the end of the year to strengthen your investment portfolio with tax savings.

When You Sell An Investment Which Has Lost Value - you have a capital loss. That loss can be used to offset capital gains. If such gains are of the short-term type, that means freeing profits from ordinary income tax. However, even where you have no gains (or have losses in excess of gains), a capital loss has tax value. Excess of loss over any gain can be used to offset other income subject to full tax - with such tax offsetting allowed up to a maximum of $1,000 in any one year. The value of such offsetting will vary depending upon your income and whether you will be filing a joint return with your spouse, a separate return, or a return as head of the household.

If you have taxable income of $20,000 and are filing a joint return, a $1,000 capital loss offset against your income will result in a net loss of $570. Tax offsetting underwrites your capital loss to the extent of $430. If you had taxable income of $50,000, tax offsetting would reduce your loss to $410. For an individual filing a separate return, tax underwriting of the loss would be even greater. Such investor with $50,000 income would find that tax underwriting reduces his $1,000 capital loss to a net loss of $280.

Because of the tax offsetting permitted, the advice often is given to review your investment portfolio at year-end with special

emphasis on your poorer investments. By taking losses sufficient to offset your gains and $1,000 of other income, taxes minimize your real loss.

Does It Pay To Take Losses Up To $1,000 A Year - allowed as a deduction against other income? As a method of weeding out your poorer investments to strengthen your portfolio, this loss realization gives maximum tax underwriting. Effect is to reduce the real loss on investment - the loss after taxes. Consider this example.

Your professional earnings produce taxable income of $25,000 a year. For five successive years, you realize excess of loss over gains in the amount of $1,000. After tax offset, your real loss in getting rid of poor investments is $2,850. You've been retaining your better investments over the same five-year period for capital appreciation. In the sixth year, you decide to take some of your profits - $5,000 - on your good investments. You keep $3,925 of $5,000 profit after capital gains tax. After subtracting your real loss of $2,850 over the first five years, you come out ahead $1,075. Before taxes, your $5,000 in losses match your $5,000 in gains, but after taxes, you come out with a profit.

Keep In Mind Tax Rules On Year-End Selling - Profits and losses on securities held for more than six months are long-term transactions. Those on securities held for six months or less are short-term transactions. Short-term losses offset short-term gains. Long-term losses offset long-term gains. If there is a net profit on one pairing and a net loss on the other pairing, the two are netted to produce a net gain or loss. If both pairings result in a loss, the two are added for a net loss. If both pairings result in a gain, the gains are kept separate. Now for the results of these pairings and any netting.

(1) If you end up with a net loss, you offset against other income up to $1,000. Any excess of loss is a short-term loss carryover available to offset gains first and then $1,000 other income for five succeeding years. (2) If you end up with a net short-term gain only, you add it to fully taxed other income. (3) If you end up with a net long-term gain only you take only half of the gain and add it to other income. However, any tax on a long-term gain can't exceed 25% under an alternative tax. If you are filing a separate return, alternative tax applies when your taxable income exceeds $18,000, $36,000 where you're filing a joint return, and $24,000 for head-of-household. (4) If you end up with both a net short-term gain and a net long-term gain, you treat each separately under tax rules (2) and (3) above.

What A Difference A Day Makes - may be a refrain from a song, but it also has tax overtones. A profit realized on a security held for six months and a day is long-term gain - a tax-favored one. Tax on such profit cannot exceed 25% and might be taxed at a rate as low as 10%. On the other hand, profit on a security held for six months or less is a short-term gain. That profit is a fully taxed one. A day's difference in holding period can make a big difference in after-tax terms.

Assume a doctor has taxable income of $25,000 and will be filing a joint return with his wife. He sells a security on which he has $1,000 profit six months after purchase. His profit is short-term. After taxes, he will keep $570 of that profit. If he held off sale for one more day, his holding period would be for more than six months. His profit would be tax-favored, long-term gain. After taxes he would keep $785 of his $1,000 profit. The difference of one day in holding period costs him $215 of his profit.

Consider the same doctor, but assume that earlier this year he realized $1,000 in short-term gains and $1,000 in long-term profits. For tax offsetting purposes, he sells securities which he held for just six months and on which he has a $1,000 loss. His loss is a short-term one and is offset against his fully taxed, short-term profits. He pays a tax of $215 on his long-term profits. If he delayed sale of securities on which he had a loss for one more day, his loss would be long-term. It would be offset against his long-term profits. That leaves him with a tax to pay on his short-term gains - and that tax would be $430.

* * * * *

When A Fee For Services Becomes Uncollectible - is the professional man entitled to a tax deduction for resulting loss of income? Generally, the answer is no. Doctors, dentists, and other professional men usually report their income on the cash basis. That means they do not report an income item until it is actually paid. The unpaid fee does represent a loss of income. However, since the professional man never reported the fee as taxable income, he is not allowed a tax deduction when it becomes uncollectible.

The same rule doesn't apply to loss of capital. Thus, when a taxpayer makes a loan which later becomes uncollectible, he is allowed a bad debt deduction. And there are a few professional men who may be allowed a deduction for loss of income due to an uncollectible fee - those who use the accrual basis. Such taxpayers report fees when earned even though they have not been paid. If a fee, previously reported as income, becomes uncollectible, a deduction for it is allowed.

On Equipment Purchased For Use In Your Practice - you may elect to take the additional "first-year depreciation allowance for small business." For Federal tax purposes, this allowance permits a purchaser to write off 20% of equipment cost in the year of purchase. That's in addition to regular depreciation. There is a misconception that this allowance can only be used by the small businessman. That isn't so. It is also available to the professional man.

Assume that a doctor normally uses the so-called straight-line method in taking depreciation. He purchases equipment with a useful life of ten years at a cost of $2,000. Without the 20% allowance, he'd take depreciation of $200 (10% of $2,000) in the first year. However, if he elects to deduct the 20% allowance, he increases first-year depreciation to $560. The 20% allowance would yield a tax deduction of $400, leaving him with a tax cost for straight-line depreciation of $1,600 ($2,000 less $400 allowance). Straight-line depreciation would yield an additional deduction of $160 (10% of $1,600). After the first year, depreciation would be limited to $160 a year. But by electing to use the 20% allowance, he increases the amount deductible in the year of purchase by $360.

This allowance creates bigger deductions in the year of purchase which allow the purchaser to recover his equipment cost more rapidly through tax offsets. Note that benefit of the allowance can be secured only if the equipment has a useful life of six or more years. Also, the allowance (in dollar amount) can't exceed $2,000 in any one year where the purchaser files a separate return, $4,000 where he files a joint return.

* * * * *

Year-End Gift Tax Reminder - By gifts of income-producing property to other family members, the donor can secure family tax savings. For instance, a gift of stock to a minor child now is possible through use of a custodian account in all of the 50 states. After such gift, dividends on the stock would be exempt from income tax until they exceeded $725 in any one year. But in making gifts, consideration must be given to current gift taxes.

One way of avoiding gift tax is to take advantage of annual gift tax exclusions by making gifts each year. There will be no gift tax if gift to a particular donee doesn't exceed $3,000-$6,000 if spouse consents to the gift. While the exclusion is a recurring one, exclusions can't be accumulated. A donor who fails to give in 1959 doesn't increase the amount available as exclusions in 1960. If you want the benefit of 1959 exclusions, you must complete gift before the end of the year.

Now available at cost—$1.50—3-ring loose-leaf binder to hold 24 monthly Lasser reports. Made of blue simulated morocco grain leather; non-soil finish with embossed cushion edge. Send check with name and address to POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Oct. 1—To St. Louis for the meeting of the American Medical Writers' Association and on the plane met Kenneth White, who heads the Chase Hotel and who took us in his car to the meeting place. There visited the exhibits during the closing hours of the meeting of the Mississippi Valley Medical Society. In the evening to confer with Ev Lyght, Van Antwerp and Austin Smith as to the future plans of the Association, for Harold Swanberg has had a coronary thrombosis and is slowly recovering.

Oct. 2—Presiding at the opening meeting of the American Medical Writers' Association, where Dr. Robert Bassett, president of the St. Louis Medical Society, welcomed the Association and excellent addresses were given. Arthur H. Wells, Duluth, editor of *Minnesota Medicine*, told of the functions of its editorial board and the manner of presenting the material, illustrating his talk with many lantern slides. Then, Theodore Van Dellen told of the *Illinois Medical Journal* and how its cover has been modified with a red band, and old Pepys said it was nice to have it red outside even if it was not read inside. Next Frederick Silber told of *Scope Weekly* and its method of conduct and how the medical news is assembled. Felix Marti-Ibanez described the concept of *MD* in a paper entitled "The fabric of a dream," but, since his throat was sore, Van Antwerp read the paper for him. Colonel John B. Coates, Jr., of the army discussed the manner in which the great medical military history is gradually coming to completion.

Richard Orr disclosed the new style manual for biologic journals which is under way, and C. E. Turner, Arlington, Massachusetts, who heads for the United States the International Union of Health Education of the Public, spoke of the written word in health education. Following the luncheon for the officers, Theodore Van Dellen told how he writes his daily health column. Colonel Frank B. Rogers, Washington, D. C., told of future plans for indexing medical literature; Walter Kahoe of the J. B. Lippincott Company spoke of the necessity for periodicals to keep up with medical progress; Dr. Donald Washburn of the dental association presented a bibliography of the dental journals of the world, and Harvey Flack described his experiences in editing the British *Family Doctor*.

Thereafter came the business meetings, and in the evening a great banquet on the Starlight Roof of the Chase Hotel. Here the Schering Corporation presented the cocktail party. Dr. George Thorn received the Honor Award for his contributions to medical literature and Dr. J. P. Gray received the Distinguished Service Award for his service to the medical profession in lecturing on medical writing in medical schools throughout the United States.

Oct. 3—This morning various conferences on the technical aspects of medical writing with representatives from the pharmaceutical houses which are now busily engaged in medical publishing—and some of it is excellent, too. Of special interest were the discussions of problems of medical translation and of the creation of medical advertising. Further discussions concerned the technics of communication involving art, films and other methods of encouraging learning. At noon with Mistress Pepys to take the train to Cincinnati, and met Oliver Lowry and his lady and dined with them on the C & O for the night run to White Sulphur Springs.

Oct. 4—Mistress Pepys' birthday, so arose early and greeted her suitably for the occasion and presented her with the orchids for which she has become of great repute. During the day in conferences, particularly on the programs for the international congresses on congenital malformations and on vaccines for poliomyelitis which will take place next year. In the evening to dine with Tom Rivers and his lady and Frank and Ina Ober.

Oct. 5-7—Three days spent constantly sitting in conferences dealing with the making of grants for research and with the giving of many fellowships in various branches of the medical sciences. In the evening dining with Tom Rivers, Mel Glasser and many others. During this period read "Virus Hunters," by Greer Williams, which is constructed along the lines of De Kruif's "Microbe Hunters" and at times even mimics that extraordinary style, and found that the author's research had been excellent and his factual data hardly susceptible to questioning. Read also a new novel of the medical profession called "The Final Diagnosis," which glorifies the place of the patholo-

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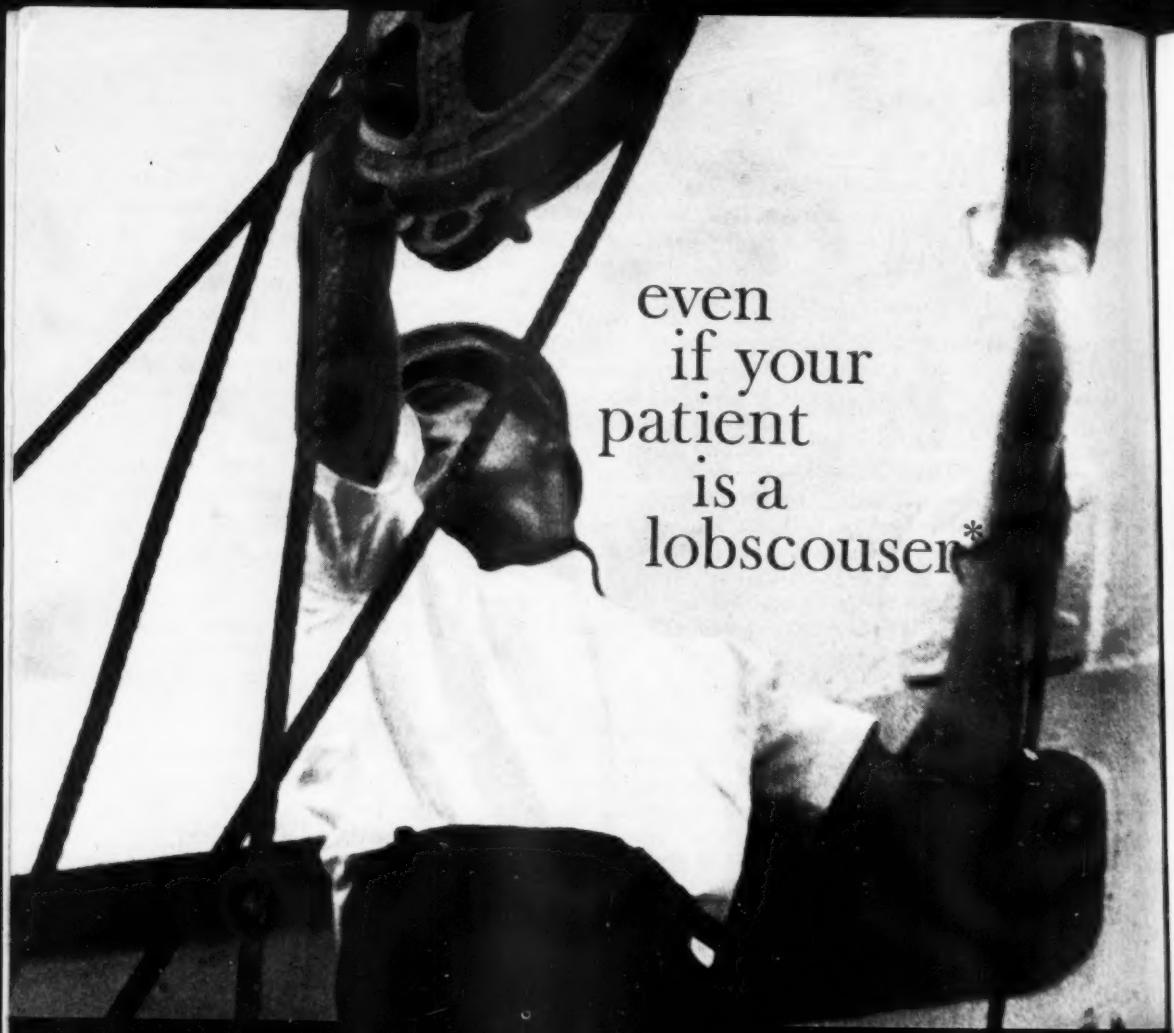

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gist in the hospital. For recreation along with these, read four mystery tales, including new ones by Ben Benson and by Erle Stanley Gardner and a British story of an escape from Dartmoor by Lourak.

Oct. 8—This morning in a conference on medical care, and then spent the afternoon witnessing the final debacle of the White Sox. In the evening met Max Geffen and conversed with him of our projects, and then by the late night train back to Chicago.

Oct. 9—On the train lay late reading a new fiction by Audrey Lindskop known as "Nicola," and she writes beautifully.

Oct. 11—Again all day at the desk and beginning to see the end of the accumulation. At night to Sinai Temple to hear Louis Mann usher in the Day of Atonement.

Oct. 12—In the evening with Charles Lawrence, the Friedells and Sam Pearlman to the opening of the opera. Thereafter to a reception for the trustees of the opera, and then to the Blackstone Hotel for a late supper, meeting members of the cast.

Oct. 13—This morning to lecture for the American Academy of Ophthalmology and Otolaryngology on "Medical writing," and met here Sam Roberts, Algernon Reese and many other leaders. At noon to the meeting of the board of the Chicago Heart Association. In the afternoon to preview a motion picture of "The Last Angry Man."

Oct. 14—In the afternoon to the Harper Library, where Fussler and Rosenthal displayed the rare books which Mistress Pepys has purchased from the Herbert Evans collection, including the first writings of Roentgen, Morgagni, William Withering and many more. Thereafter to the Quadrangle Club, where came Mrs. Kimpton, Vice-Chancellor Kirkpatrick and many others of the faculty, Leo Zimmerman, Ilza Veith, and visitors from other medical schools, including the Sheehans from Loyola.

Oct. 15—This morning an interview on wine and at noon to lunch with Algernon Reese, discussing problems of medical writing and editing. Then late to the Capitol Limited for a trip to Martinsburg, West Virginia, with Mistress Pepys. En route reading "The Status Seekers," which is sociology for the masses and began reading the 700 page novel by Robert Ruark entitled "Poor No More," and while it has a good deal of color and flash, it makes but little impression on the cortex.

Oct. 16—Early in the morning to the train came E. Andrew Zepp, who is the secretary-treasurer of the postgraduate institute, and he was clad in the costume suitable to the delivery room and had left a patient in progress to meet the train. To the Shenandoah Hotel and then to Shepherdstown to speak to a great convocation of students and faculty of Shepherd College on the subject of marriage. At the College was introduced by President Ikenberry. Thereafter to Harpers Ferry, and in the Hilltop House a panel considered the whole Harpers Ferry incident. My friend J. C. Furnas, who has just written "The Road to Harpers Ferry," was an honored guest and with him Senator Randolph and others.

So then back to Martinsburg in time to hear M. E. Lichtenstein speak on hernia and John C. Krantz on anesthetics. At dinner the speaker was Drew Pearson, and old Pepys was called on to make the introduction and spoke of Pearson's contribution to the science of reporting. Now meeting Dr. William R. McCune, who is president of the Eastern Panhandle Medical Society, and Dr. Wanger, who as secretary and major-domo has conceived a technic for making a powerful program. He, a graduate of the University of Illinois College of Medicine, is married to Dr. McEldridge, who is a graduate of Rush Medical College.

Next with Pearson and many others to the high school at Harpers Ferry to see a pageant called "The Prophet," which was the story of John Brown.

Oct. 17—To preside at the opening of this great clinical program, which included papers on renal failure by Burnett, on viral and bacterial diseases of the upper respiratory tract by Gibson of Tufts, and on the importance of examining the feet in physical diagnosis by Louis A. M. Krause, University of Maryland. Then an address by Perry S. MacNeal, University of Pennsylvania.

In the evening a great banquet filling all the available space, and here old Pepys spoke of medicine and the changing social order. One practitioner said the going fees for his area in West Virginia were $2.00 for office calls and $3.00 for home calls—and he seemed to be doing well. Spoke also to Dr. and Mrs. Myer Bogarad of Weirton, West Virginia, who had driven some 250 miles to participate in this postgraduate conference. Then came a pleasant dance, which must have lasted long after old Pepys retired for the day.

(Continued on page A-204)

Oct. 18—Early to the penthouse home of Lou Cohen to view his art treasures and then to drive far out to visit an apple orchard. Returning, found M. Edward Davis, who had made a hasty trip from Chicago to participate in this graduate instruction. At noon a luncheon where old Pepys presided, introducing Raymond Massey after an hour of conversation with him. And here also was Mrs. Cavelier, who staged the great production of "The Prophet." Next with the ladies to visit the beautiful home of the Cheesemans, and at the tea both Mistress Pepys and Pepys spoke of the aid that the auxiliary gives to the medical profession. Thereafter with Dr. Zepp to visit his home and to meet his wife and son and to hear stories of practice in the panhandle. After that to meet the Capitol Limited and embark for the return to Chicago.

Oct. 19—At the desk all this day and in the evening to dine at the Tower Club, accompanied by Dean George V. LeRoy and his lady. Then to hear the opera "Cenerentola," by Rossini.

Oct. 20—At noon to a luncheon in the Hotel Sherman, where Karl Meyer presided and there came many others to consider the development of the great "Salute to Medical Research." In the afternoon to station WAIT for an interview by Phil Lind. In the evening to Edmund Jacobson's to a dinner of steak and champagne.

Oct. 21—This day late to the Hotel Morrison, where some 500 people assembled for the great banquet of the American Occupational Therapy Association. Miss Willard of the University of Pennsylvania presided. A citation was given to Colonel Ruth A. Robinson of Walter Reed Hospital, Washington, D.C. Old Pepys spoke on the subject "Health through work" and congratulated Beatrice Wade, Marjorie Fish and the other occupational therapists on the fine state to which they have brought their organization.

Oct. 22—At noon to the Conrad Hilton Hotel to speak in the Boulevard Room to the occupational health nurses on "Safety." Presiding was Happy Bruder, and here were many occupational nurses who work in the industrial plants of the Chicago area. In the evening with Mistress Pepys and Carmen Gutierrez to hear the Chicago Symphony in a rendition of a Stravinsky operetta and two compositions by Respighi.

Oct. 23—At noon with M. Friedell and attorney Sol Hoffman to the Standard Club for a conference. In the evening to Ballantine's, where some 100 Phi Delta Epsilon members, together with proposed pledges, had assembled. Old Pepys was introduced by Donald Aaronson and spoke on the future of medicine.

Oct. 24—By the early jet plane to Boston in two hours. Then, by car to the Lawrence Hospital in Medford, Massachusetts, and met Mayor Carr, chairman of the board Gallagher, and also Mrs. Gallagher and their son. So toured the hospital's new addition and found it excellent. Thereafter to speak to several hundreds in a tent erected on the lawn and after that by jet plane to Chicago in two hours and 30 minutes. En route finished "Poor No More" and concluded the book is greatly overdone and unnecessarily verbose.

Oct. 25—All this day with the accumulations on the desk and found the periodicals containing more and more material worthy of reading and thus taking much longer to read.

Oct. 26—All this day spent at the desk, in particular editing new articles contributed to the "Britannica Book of the Year" and finding that medicine has made great progress this year. Cancer research has been greatly intensified and the work in biogenetics is so complex that a full comprehension is difficult. Reading also Louise Cross' book "The Preparation of Medical Literature," and found it somewhat of a consensus of material derived from other similar works on the subject.

With Theodore Cornbleet and his lady to dine at the Tower Club and then to hear "Simon Boccanegra."

Oct. 27—With Charles Haney by the early plane to Des Moines and then driving to Grinnell. Here to visit the hospital, which is some 41 years old and, like all such ancient structures, utterly inadequate for modern needs. Then to the college and inspected the new library, which is the maximum of modernity. To the office of President Bowen and there sat with the student council discussing such questions as the placement of dormitories. Next to the great gymnasium, where some 600 assembled for dinner, and spoke to them of the need for a hospital comparable to the library. Following the address to the beautiful and tasteful home of Dr. Parish, and here were members of the faculty. So we gossiped until late and at 2:30 A.M. took the Rocket back to Chicago.

(Continued on page A-206)

What IS The Truth About Dietary Fats?

Recently a great deal of interest has been aroused on the question of a possible etiologic link between the ingestion of food fats and pathophysiologic changes in certain body tissues.

Basic research on this problem is being carried on throughout the world, the approach ranging from animal experimentation to biochemistry, to ethnological statistics.

In a number of instances the lay press has prematurely reported the findings of one research group or another, *without the benefit of unbiased competent evaluation*. Some scientific as well as lay articles have attempted to correlate inconclusive, fragmentary, and conflicting results, frequently leading to undesirable confusion.

The problem, however, is far from settled. If final results of this world-wide research establish beyond reasonable scientific doubt that fat intake is directly related to degenerative disease, accurate information should be provided for the profession so that in turn the public may be properly enlightened.

On the other hand, if conclusive evidence points to little or no etiologic relationship between fat ingestion and degenerative disease, it will become difficult for the scientific world to counteract the cumulative effects of misinformation on the public mind.

Furthermore, evidence is accumulating to indicate that lowering of the plasma cholesterol by limitation of dietary fat and by administration of unsaturated fatty acids may actually increase the deposition of cholesterol in the tissues.[1]

The obvious need at present is for basic research and proper evaluation as well as unprejudiced correlation of findings from all quarters, so that the medical profession as well as the public may be protected from the publicizing of premature and unwarranted conclusions.

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1. Kuhl, W. J., Jr., and Cooper, J.: Exchangeable C^{14}-Cholesterol Pool Size as an Index of Cholesterol Metabolism: Effect of Low Fat and Highly Unsaturated Fat Diets, Proc. Cen. Soc. Clin. Res., J. Lab. & Clin. Med. *52*:919 (Dec.) 1958.

STATEMENT BY NATIONAL RESEARCH COUNCIL

"A large amount of information has been made available in recent years relating fats to the causation of atherosclerosis, coronary artery disease, and other similar diseases. However, the data are so incomplete and conflicting that it is impossible to draw conclusions which are universally acceptable to nutritionists and medical authorities."

"Until it is clearer which fats are more desirable nutritionally and which, if any, are undesirable—major changes in American dietary habits are not to be recommended."

▪

The Role of Dietary Fat in Human Health: National Academy of Sciences—National Research Council, Washington, D. C., Publication 575, 1958.

American Meat Institute
Main Office, Chicago...Members Throughout the United States

Oct. 28—In the afternoon at the home of Mrs. Don to meet some 70 ladies and to discuss for them some new research in the Hektoen Institute, to which the Weissmann Foundation makes such a significant contribution. In the evening with Mistress Pepys to a dinner dance of the Lion's Clubs of our Chicago area, held to honor Dr. Morris T. Friedell and Dr. Novak, who were founders of one of the Lion's Clubs. Old Pepys spoke to them of the work of a physician as a citizen.

Oct. 29—By the early morning plane to New York and to lunch with William and Stanley Lasdon at the Four Seasons. Meanwhile, Mistress Pepys entertained 8 or 10 of our lady friends from New York at the Lotus Club, where Cornelia Otis Skinner spoke and read from her works. In the afternoon came Peter Warren and Ted Gotthelf to talk about some new methods of medical communications.

In the evening came Milton and Sylvia Lasdon to dine and after that to the new auditorium built at Memorial Hospital, where Richard Orr presided and old Pepys spoke to 100 members of the New York chapter of the American Medical Writers' Association. Here greeted again Lois Stice, Larry Salter, Mrs. McQueen-Williams of *MD*, Fred Silber of *Scope Weekly*, and associates of practically all of the medical publications of the New York area.

Oct. 30—To breakfast came Stanley Henwood and after that Max Geffen and Bill White, and our discussions carried on through the luncheon period. Then to Doubleday for a great meeting with Runyon, Stuttman, Beebe, Evans, Whittemore and others to design a new work. Next, by the late train to Washington, D. C.

Oct. 31—In Washington, D. C., at the Mayflower and early to the meeting of the Mid-Atlantic Chapter of the American Medical Writers' Association. Here Israel Light operated the tape recorder and Dr. Henry J. L. Marriot, Baltimore, presided and spoke of medical writing. On the morning program were John Troan and old Pepys, and on the afternoon program were Gerald Gross, Geoffrey Edsall and Michael Amrine. Also here were Odenwald, Florence Cooksley and Al Rubin. In the evening with Mary Switzer and Isabel to Pierre's to dine and then to the National Theater, where Shirley Booth, Carol Haney and some youngsters appeared in William Inge's significant new play "The Loss of Roses."

RICHARD ARMOUR

PUZZLING CASE

The patient who was kind and cheerful,
Cooperative, willing,
Is all on edge, distraught and tearful,
And in a mood for killing.

The patient who for days was jolly
And thoughtful of the nurses
Is mean as he can be, by golly,
And quick with frightful curses.

No need to call a consultation,
A huddle grim and formal.
The patient's giving indication
Of getting back to normal.

PSYCHIATRISTS

Psychiatrists instead of ouches
Hear patients yakking on their couches.
Instead of soothing sundry pains,
They try to calm disordered brains.

They delve into the lurking id
That keeps itself so shyly hid,
And, though it might give satisfaction,
Can't tie an ego up in traction.

Psychiatrists don't cut or stitch,
Though sometimes they must have the itch,
But have to grapple and to grope
Without x-ray or fluoroscope,

And look inside not head or lung
But books by Adler, Freud and Jung.

Official Journal of the Interstate Postgraduate Medical Association

Volume 26, Number 6 **DECEMBER 1959**

Postgraduate Medicine

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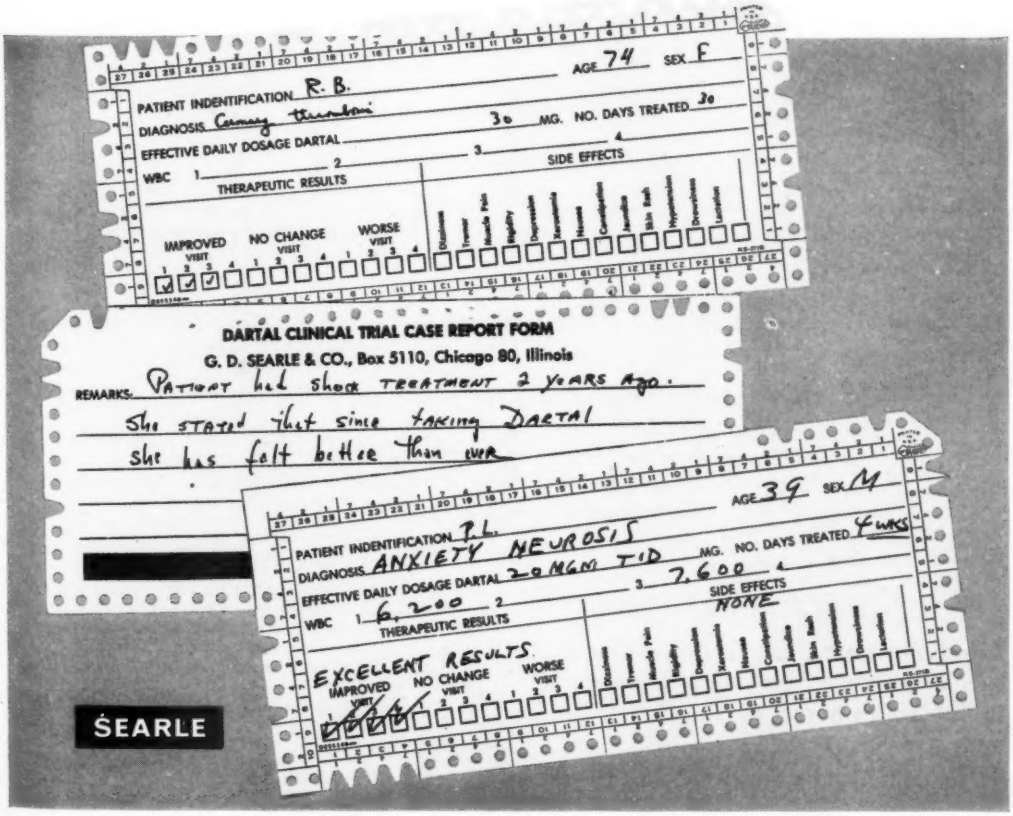
	Hypertensive Cardiovascular Disease	14	13

with low dosage: Only one tablet of 2 or 5 or 10 mg. t.i.d.
with relative safety: Evidence indicates that Dartal is not icterogenic.

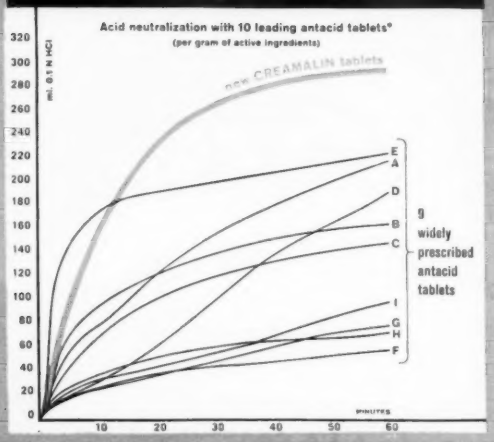

PATIENT INDENTIFICATION R. B.
AGE 74 SEX F
DIAGNOSIS Cerney thrombosis
EFFECTIVE DAILY DOSAGE DARTAL 30 MG. NO. DAYS TREATED 30
WBC 1 2 3 4 SIDE EFFECTS
THERAPEUTIC RESULTS
IMPROVED NO CHANGE WORSE
VISIT
DARTAL CLINICAL TRIAL CASE REPORT FORM
G. D. SEARLE & CO., Box 5110, Chicago 80, Illinois
REMARKS: PATIENT had shock TREATMENT 2 YEARS AGO.
She STATED that since taking DARTAL
she has felt better than ever
PATIENT INDENTIFICATION P. L.
AGE 39 SEX M
DIAGNOSIS ANXIETY NEUROSIS
EFFECTIVE DAILY DOSAGE DARTAL 20 MGM TID MG. NO. DAYS TREATED 4 WKS
WBC 1 6,200 2 3 7,600 4 SIDE EFFECTS NONE
THERAPEUTIC RESULTS
EXCELLENT RESULTS
IMPROVED NO CHANGE WORSE
VISIT
SEARLE

THE MOST SIGNIFICANT IMPROVEMENT IN ANTACID THERAPY SINCE THE INTRODUCTION OF ALUMINUM HYDROXIDE IN 1929

NEW Creamalin ANTACID TABLETS

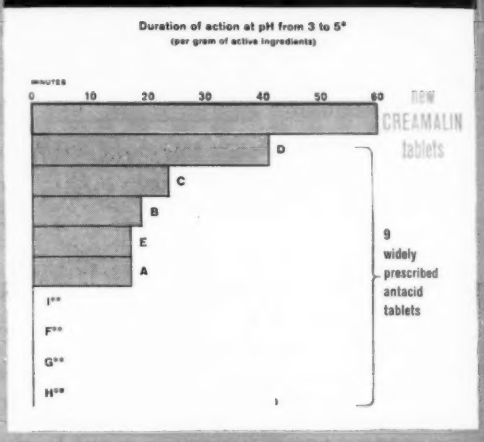
CREAMALIN NEUTRALIZES *MORE* ACID *FASTER*

Quicker Relief · Greater Relief



CREAMALIN NEUTRALIZES *MORE* ACID *LONGER*

More Lasting Relief



Tablets were powdered and suspended in distilled water in a constant temperature container (37°C) equipped with mechanical stirrer and pH electrodes. Hydrochloric acid was added as needed to maintain pH at 3.5. Volume of acid required was recorded at frequent intervals for one hour.

*Hinkel, E. T., Jr., Fisher, M. P. and Tainter, M. L.: A new highly reactive aluminum hydroxide complex for gastric hyperacidity. To be published.
**pH stayed below 3.

Each Creamalin Antacid Tablet contains 320 mg. specially processed, highly reactive, short polymer dried aluminum hydroxide gel, (stabilized with hexitol), with 75 mg. magnesium hydroxide.

1. *Neutralizes acid faster (quicker relief)*
2. *Neutralizes more acid (greater relief)*
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4. *No constipation · No acid rebound*
5. *More pleasant to take*

No chalky taste. New CREAMALIN tablets are not chalky, gritty, rough or dry. They are highly palatable, soft, smooth, easy to chew, mint flavored.

Adult Dosage: Gastric hyperacidity—2 to 4 tablets as necessary. Peptic ulcer or gastritis—2 to 4 tablets every two to four hours. Tablets may be chewed, swallowed with water or milk, or allowed to dissolve in the mouth.

Supplied: Bottles of 50, 100, 200 and 1000.

Winthrop LABORATORIES · NEW YORK 18, NEW YORK

In prophylaxis of angina pectoris

The best results . . ."

"The best results . . . in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE]. . . ." Russek[1] so reported using double-blind methods in an important new study of pentaerythritol tetranitrate, a placebo, meprobamate, and EQUANITRATE.

EQUANITRATE reduces the frequency and severity of attacks and controls angina-triggering emotions.

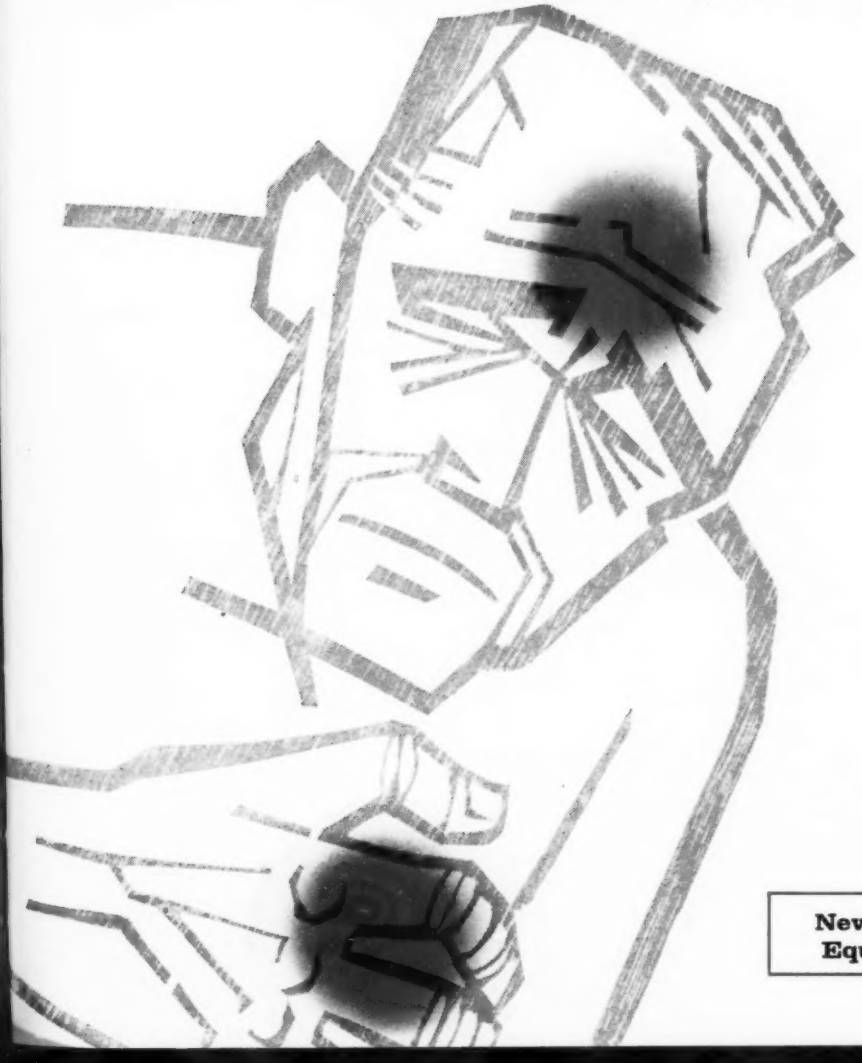
Supplied: EQUANITRATE **10** (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE **20** (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

1. Russek, H.I.: Am. J. Cardiol. *3*:547 (April) 1959.

Equanitrate*

Meprobamate and Pentaerythritol Tetranitrate, Wyeth

Wyeth
Philadelphia 1, Pa



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help prepare your middle-aged patients for healthy retirement years

each KAPSEAL *contains:*

vitamins	
Vitamin A	1,667 Units (0.5 mg.)
Vitamin B_1 mononitrate	0.67 mg.
Ascorbic acid	33.3 mg.
Nicotinamide	16.7 mg.
Vitamin B_2	0.67 mg.
Vitamin B_6	0.5 mg.
Vitamin B_{12} with intrinsic factor concentrate	0.033 USP Unit (oral)
Folic acid	0.1 mg.
Choline bitartrate	6.67 mg.
Pantothenic acid (as the sodium salt)	5 mg.
minerals	
Ferrous sulfate (exsiccated)	16.7 mg.
Iodine (as potassium iodide)	0.05 mg.
Calcium carbonate	66.7 mg.
digestive enzymes	
Taka-Diastase® (aspergillus oryzae enzymes)	20 mg.
Pancreatin	133.3 mg.
protein improvement factors	
l-Lysine monohydrochloride	66.7 mg.
dl-Methionine	16.7 mg.
gonadal hormones	
Methyl testosterone	1.67 mg.
Theelin	0.167 mg.

dosage: One Kapseal three times daily before meals. Female patients should follow each 21-day course with a 7-day rest interval.

packaging: ELDEC KAPSEALS are available in bottles of 100.

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FORTHCOMING FEATURES

IN Postgraduate Medicine

In January

A SPECIAL ISSUE FROM

University of Michigan Medical School

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Guest Editor

FOR ALL ARTHRITICS — ESPECIALLY

...THE 15 TO 30 PER CENT WHO CANNOT TOLERATE THERAPEUTIC DOSAGES OF ORDINARY SALICYLATES[1]

...THE 25 TO 45 PER CENT WHO SUFFER SIDE EFFECTS WITH PHENYLBUTAZONE[2]

...THE UP TO 85 PER CENT WHO SUFFER SIDE EFFECTS WITH STEROIDS[3]

NEW ARTHROPAN T.M. LIQUID

BRAND OF CHOLINE SALICYLATE

BYPASSES THERAPEUTIC HAZARDS

ARTHROPAN LIQUID contains Choline Salicylate, a newly synthesized molecule. It is not a combination drug, nor a buffered compound. It reduces inflammation, provides analgesia, enhances mobility. Chief among its clinical properties is unexcelled tolerance, which permits patients—even many with gastric sensitivity—to take the massive salicylate dosages so necessary in the treatment of arthritic states. Peak salicylate blood levels are reached 12 times faster than with aspirin, yet sustained blood levels equal those of aspirin. Therapy with ARTHROPAN alone may be sufficient even for patients previously on steroids or phenylbutazone, or may permit reduced dosage of these more potent agents. ARTHROPAN is provided in an exceptionally palatable liquid, which explains the high degree of patient acceptance.

SUPPLIED: 16 oz. and 8 oz. bottles. Each ml. of ARTHROPAN LIQUID contains 174 mg. of Choline Salicylate. Each teaspoonful (5 ml.) contains 870 mg. of Choline Salicylate.

REFERENCES: 1. Product Data Brochure, Medical Department, The Purdue Frederick Company, New York 14, N. Y., 1959. 2. Goodman, L. S., Gilman, A.: The Pharmacological Basis of Therapeutics, 2 ed., New York, The Macmillan Company, 1955, p. 322. 3. Goodman, L. S., Gilman, A.: op. cit., p. 1681.

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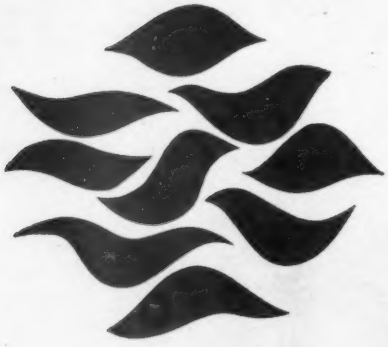

in eight years Novahistine hasn't cured a single cold—but it has brought prompt relief of symptoms to almost 8,000,000 patients*

With the introduction of Novahistine, a better and safer way to relieve symptoms of a cold became available to physicians. The synergistic action of the Novahistine formula...combining an orally-effective vasoconstrictor with an antihistamine...promptly clears the air passages and checks irritant nasal secretions. NOVAHISTINE can eliminate the problem of rebound congestion and damage to nasal mucosa in patients who misuse topical applications. • For long-lasting "Novahistine Effect" prescribe Novahistine LP Tablets...which begin releasing medication as promptly as conventional tablets but continue bringing relief for 8 to 12 hours. Two Novahistine LP Tablets in the morning and two in the evening will effectively control the average patient's discomfort from a cold. Each tablet contains phenylephrine HCl, 20 mg., and chlorprophenpyridamine maleate, 4 mg.

*Based on National Prescription Audits of new Novahistine prescriptions since 1952.

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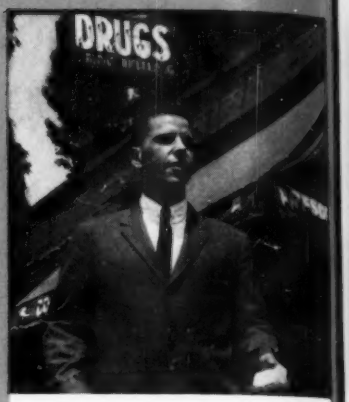
Next day on the job I was a total loss — could hardly lift a slide rule!



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FOR PAIN

Amazing! The pain went away fast — in about 15 minutes. I slept like a baby. Finished my design for the new warehouse next day, and not a bit of trouble since!

ACTS FASTER — usually within 5-15 minutes. **LASTS LONGER** — usually 6 hours or more. **MORE THOROUGH RELIEF** — permits uninterrupted sleep through the night. **RARELY CONSTIPATES** — excellent for chronic or bedridden patients. **VERSATILE** — new "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

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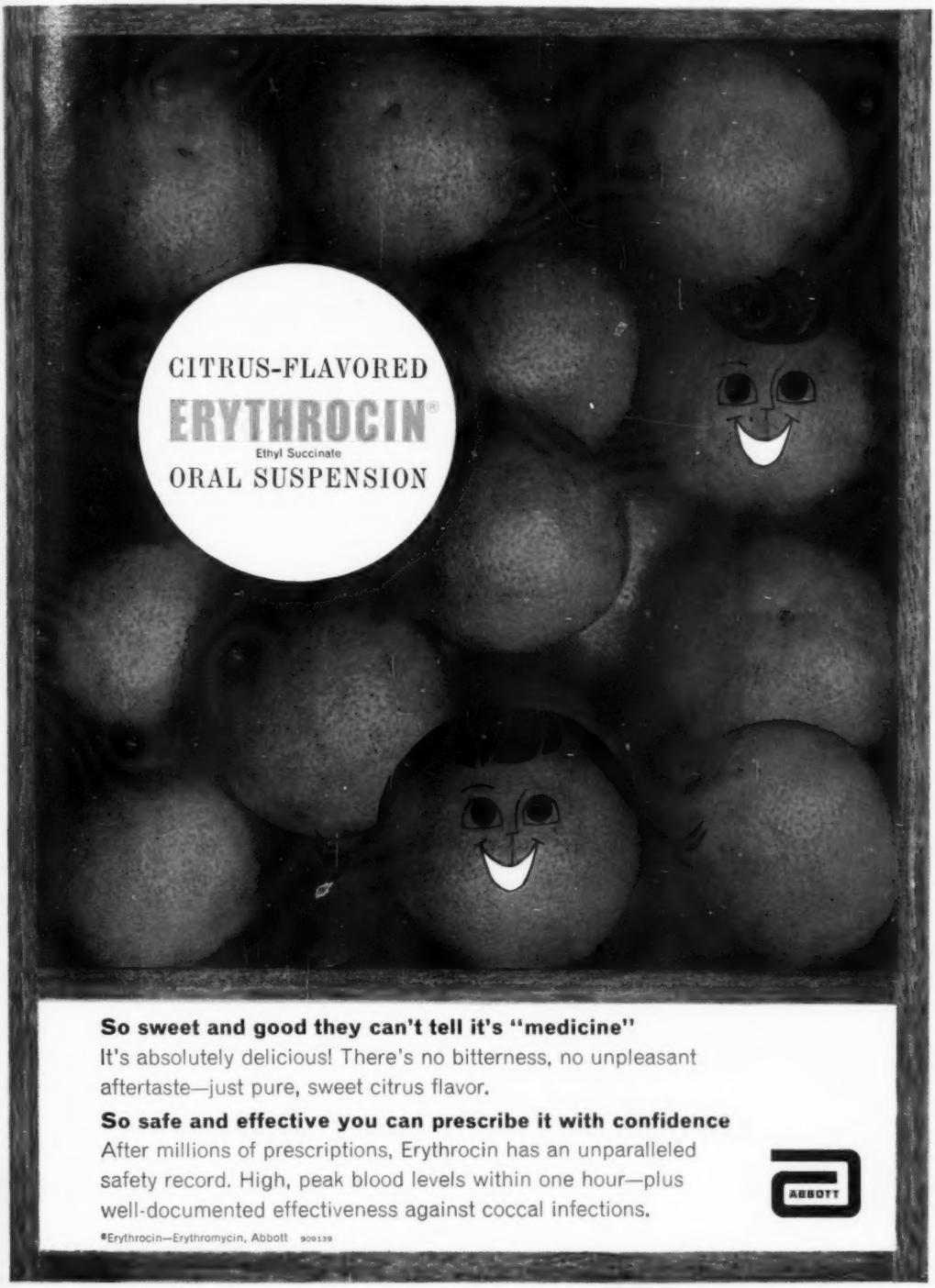

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removes depression[1-4]

the true antidepressant

rapidly effective

antidepressant response often within a few days; complete remission within 2-6 weeks, in 4 out of 5 patients.[1-3]

corrective

removes mild-to-severe depressions and anxiety-tension fatigue rather than merely masking the symptoms as do tranquilizers, CNS stimulants or sedatives.[1-3]

safe

in 3 years of rigorous clinical trials and in thousands of recorded cases to date, there have been no significant reports of toxicity to liver, kidneys or blood and side effects have been only occasional or mild.[1-4]

simple dosage schedule:

1 tablet 3 times a day.

Indications: Nardil is indicated in the office treatment of all mild to severe depressions; in those related to childbirth, menopause, old age, or those caused by stress situations; when there is a past history of depressed periods, and in depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis.

Dosage: One tablet three times a day.

The above dosage should be maintained until remission of symptoms is achieved which may require 2 to 6 weeks. Dosage should then be reduced to a maintenance level of one or two tablets a day.

Supplied: 15 mg. orange-coated tablets, bottles of 100.

References: **1.** Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc. 80:* Art 3: 780 (Sept. 17) 1959. **2.** Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System 20*:197 (May) 1959. **3.** Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat. 116*:71-72 (July) 1959. **4.** Arnow, L. E.: Phenelzine: A Therapeutic Agent for Mental Depression, *Clinical Med. 6*:1573 (Sept.) 1959. **5.** Dickel, H. A.; Dixon, H. H.; Shanklin, J. G., and Dixon, H. H., Jr.: Tension Fatigue States and Their Adjunctive Treatment Using Nardil, *Clinical Med. 6*:1579 (Sept.) 1959.

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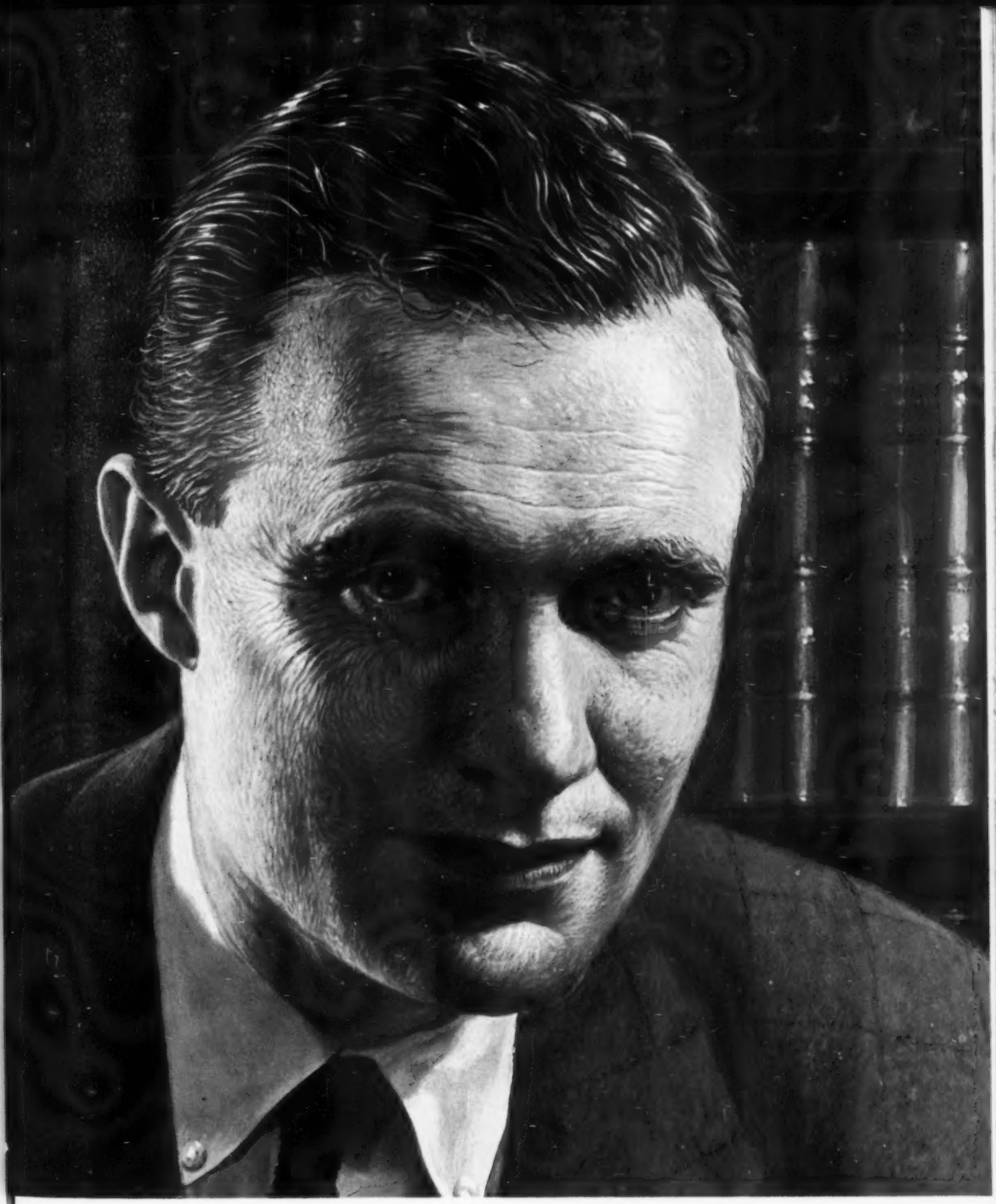

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cadron helps restore a "natural" sense of well-being

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one 0.75 mg. tablet of **Decadron** (dexamethasone) replaces:

↓ One 4 mg. tablet of	↓ One 5 mg. tablet of	↓ One 20 mg. tablet of	↓ One 25 mg. tablet of
methylprednisolone or triamcinolone	prednisolone or prednisone	hydrocortisone	cortisone

SUPPLIED: As 0.75 mg. scored pentagon-shaped tablets. Also as 0.5 mg. tablets, to provide maximal individualized flexibility of dosage adjustment, since many patients achieve adequate control even on lower dosage.

Detailed literature is available on request.
DECADRON is a trademark of Merck & Co., Inc.

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TINY TABLET UNDER TONGUE
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ANYTIME, ANYWHERE, WITHOUT NEED EVEN FOR A GLASS OF WATER

because prodromal warning usually tells patients that the time to arrest imminent migraine attack is right now, and the place to do it is right here.

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MORE CONVENIENT... NO WATER, INJECTIONS OR PRIVACY NEEDED

All the patient has to do is to place a tiny ERGOMAR tablet under tongue. It enters blood stream directly through buccal lining, bypasses stomach and hepatic system and aborts vascular headache and migraine in approximately one half the usual time of ingested tablets.[1-3]

Dosage: Sublingually, 1 tablet at onset of attack. Additional doses may be taken, if necessary, as follows: 1 tablet every half-hour until relief is obtained. Total dosage must not exceed 3 tablets within 24 hours.

Contraindications: Peripheral vascular and coronary heart disease, hypertension, renal or hepatic dysfunction and pregnancy.

Supplied: ERGOMAR Tablets, 2 mg. ergotamine tartrate per tablet, in specially developed dispenser packages of 12 tablets. *May we suggest for patient convenience and economy, writing for not less than 12 tablets in a prescription.*

References: **1. DeJong, R. N.: GP *19*:147, 1959. 2. Scientific Exhibit, 9th Annual Meeting, Am. Acad. Neurology, Boston, Mass., April 22-27, 1957. 3. Berman, B. A.: Current personal communication in the files of Nordson Laboratories. 4. Saunders, S. H.: Current personal communication in the files of Nordson Laboratories. 5. Blumenthal, L. S., and Fuchs, M.: Am. Acad. Neurology, Los Angeles, Calif., April 15-18, 1959. *Sublingual Administration of Ergotamine in Relief of Migraine and Vascular Headache.***

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in 400 mg. continuous release capsules as

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JUST ONE CAPSULE LASTS ALL DAY

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MILTOWN® continuous release capsules

HIGHER POTENCY FOR GREATER CONVENIENCE

- relieves *both* mental and muscular tension without causing depression
- does not affect autonomic function
- does not impair mental efficiency, motor control, or normal behavior

Usual dosage: One capsule at breakfast, one capsule with evening meal

Available: *Meprospan-400*, each blue capsule contains 400 mg. Miltown (meprobamate)

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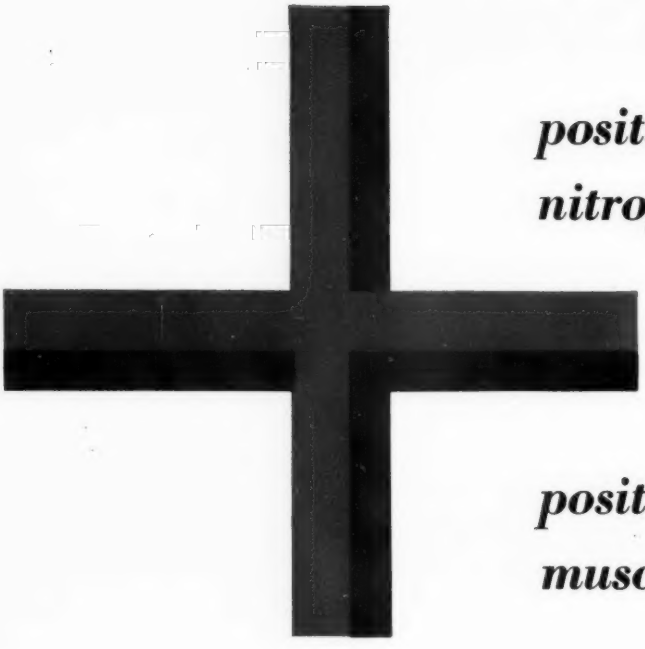
Both potencies in bottles of 30.

WALLACE LABORATORIES, *New Brunswick, N. J.*

CMC-3429



positive
nitrogen balance

positive
muscular growth,

positive, objective gains for

DURABOLIN, ***a new, well-tolerated, long-acting biologic stimulant,*** has demonstrated dramatically that the progress of many negative clinical conditions can be halted or reversed. In more than three years of clinical study in Europe, Canada and the United States, positive *measurable* benefits have been induced after even short-term DURABOLIN therapy.

DURABOLIN (nandrolone phenpropionate injection, Organon) acts as a potent tissue-builder by rapid establishment of a positive nitrogen balance through more efficient utilization of dietary protein. The weight gain resulting from marked appetite improvement takes the form of solid, lean tissue without edema.

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Durabolin®

Nandrolone phenpropionate injection, Organon

your patients' well-being

porosis, osteogenesis imperfecta, and slow-healing, uncomplicated fractures. These actions make DURABOLIN a valuable palliative in inoperable mammary cancer with skeletal metastases.

DURABOLIN is also indicated as an adjunct to chemo-therapeutic or surgical measures in which a catabolic state has been induced, e.g., during long-term corticosteroid regimens, to prevent excessive nitrogen loss following major operations, and to reduce the serum level of nitrogenous waste products in uremia.

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prevent "morning sickness" the night before...

Bendectin

(2 tabs. h.s.)

Just 2 Bendectin tablets at bedtime. In clinical trials,[1-3] this dosage schedule relieved morning sickness symptoms in more than 95% of cases.

Bendectin combines three complementary therapeutic actions: antispasmodic/antinauseant/pyridoxine supplementation to *prevent* this annoying discomfort.

1. Nulsen, R. O.: Ohio State Med. J. *53*:665, 1957. 2. Personal communications: 1956-57.
3. Towne, J. E.: Internat. Rec. of Med. *171*:584, 1958.

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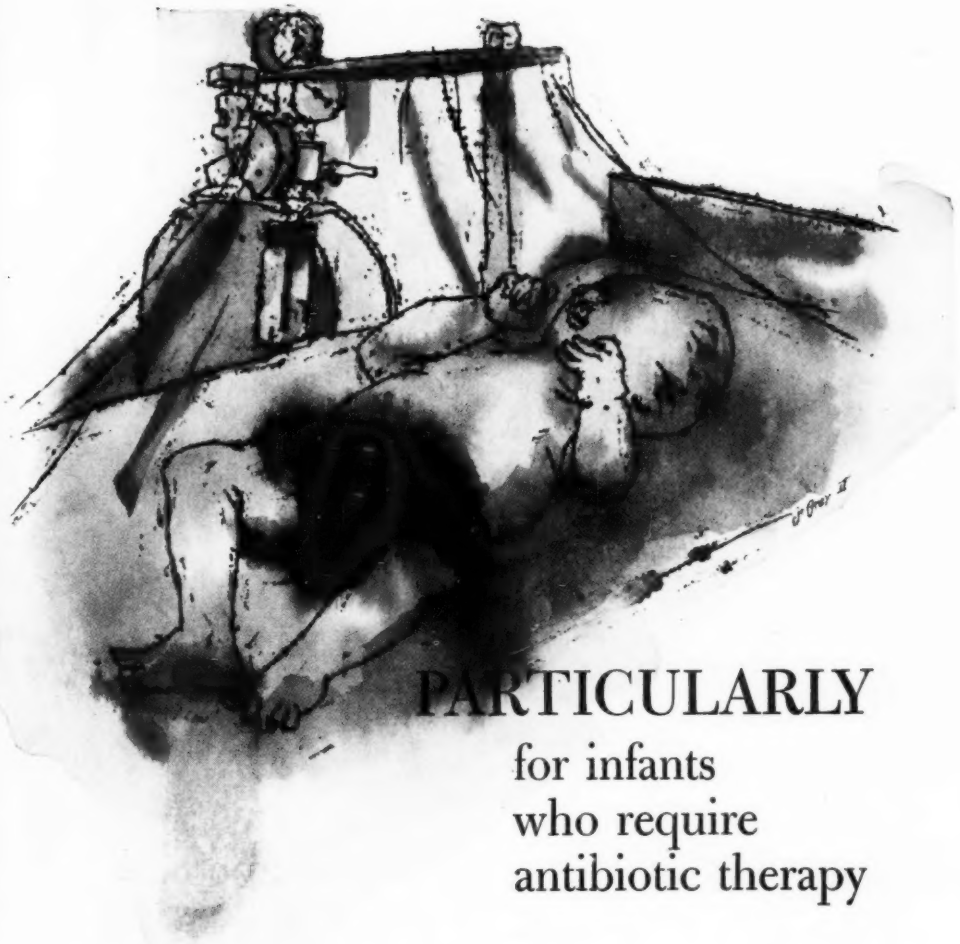

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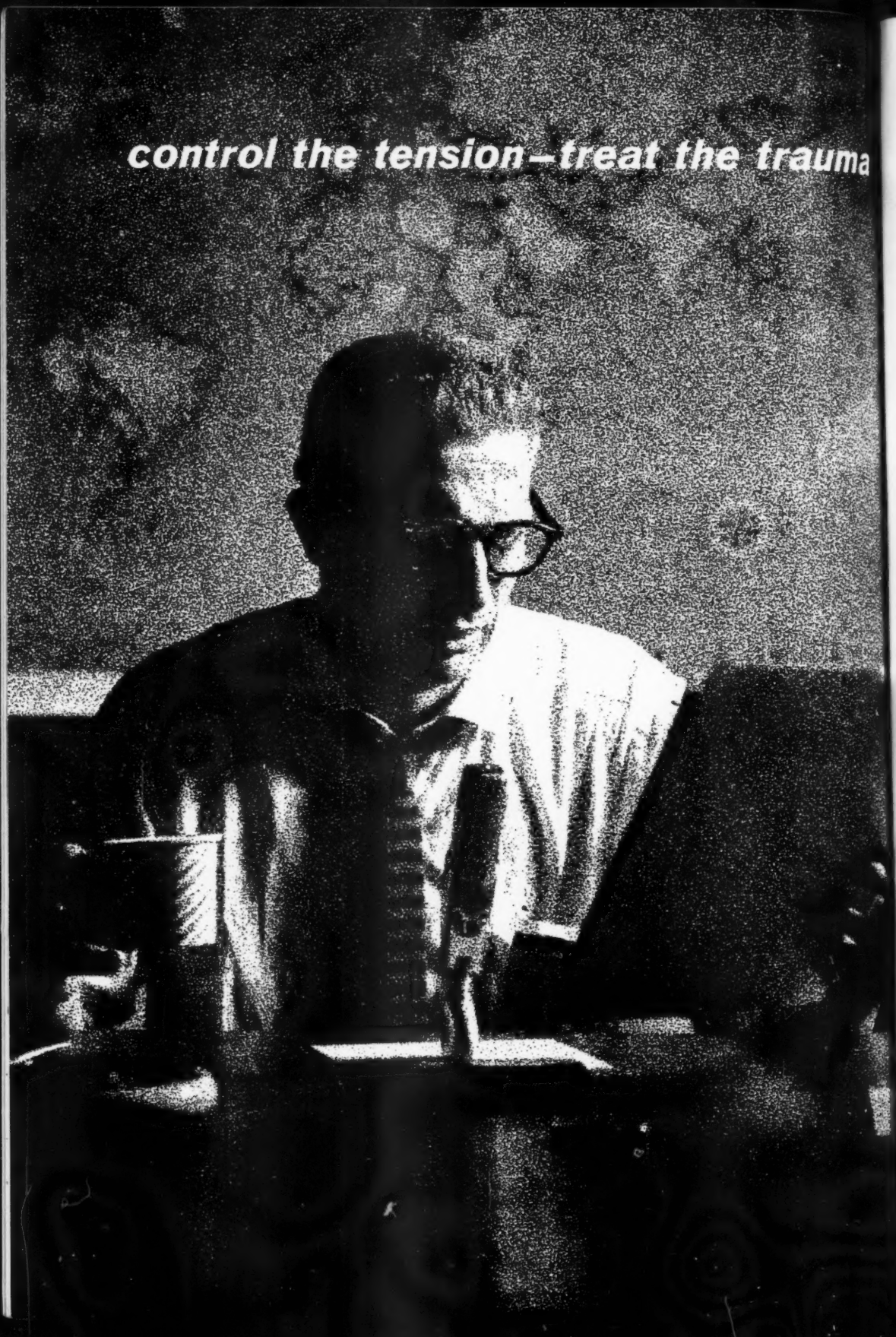
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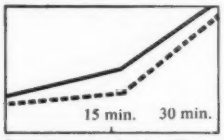
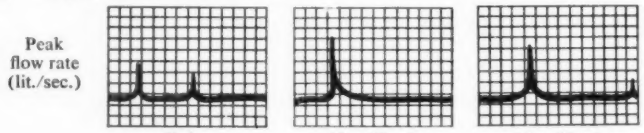


Vital capacity increase of 30.6% in 30 minutes—average of 69 patients.[1,5,6]

Maximum breathing capacity increase of 25.7% in 30 minutes—average of 49 patients.[5,6]

Improved cough efficiency as shown in a patient with bronchial asthma following Elixophyllin dosage of 75 cc.:[7]



Volume exhaled (liters) increased from 0.076 to 0.391 after 30 minutes, and to 0.805 after 60 minutes.

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1. Spielman, D.: Ann. Allergy 15:270, 1957. **2.** Schluger, J. et al.: Am. J. Med. Sci. 234:28, 1957. **3.** Kessler, F.: Connecticut St. M. J. 21:205, 1957. **4.** Greenbaum, J.: Ann. Allergy 16:312, 1958. **5.** Frank, D. E.: Antibiotic M. 6:338, 1959. **6.** MacLaren, W. R.: To be published. **7.** Bickerman, H. A. et al.: Sci. Exh., A.M.A. Convention, June 1959.

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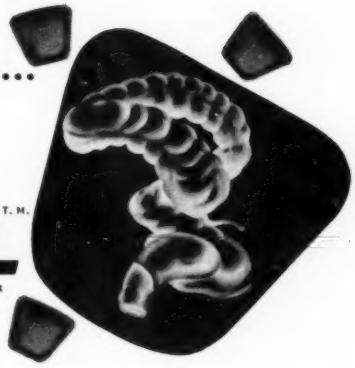

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References: (1) Kaindl, F.; Samuels, S. S.; Selman, D., and Shaftel, H.: Angiology *10*:185-192 (August) 1959. (2) Kaindl, F.; Pärtan, J., and Polsterer, P.: Wien. klin. Wchnschr. *68*:186, 1956. (3) Brucke, F., et al.: Wien. klin. Wchnschr. *68*:183, 1956. (4) Nash, C. B.; Drinnon, V., and Clark, B. B.; abstracted, Fed. Proc. *17*:397 (March) 1958. (5) Singer, R.: Wien. med. Wchnschr. *107*:734-736 (Sept.) 1957. (6) Dungan, K. W., and Lish, P. M.; abstracted, Fed. Proc. *17*:365 (March) 1958. (7) Billiottet, J., and Ferrand, J.: Semaine méd. *34*:635-637 (May) 1958.

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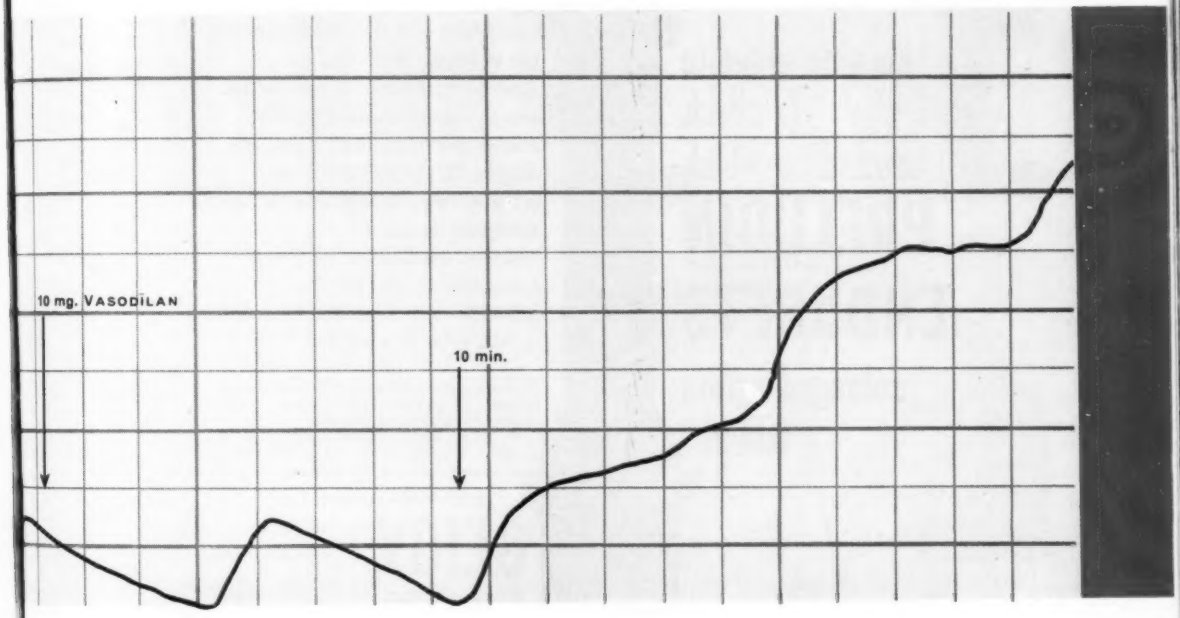

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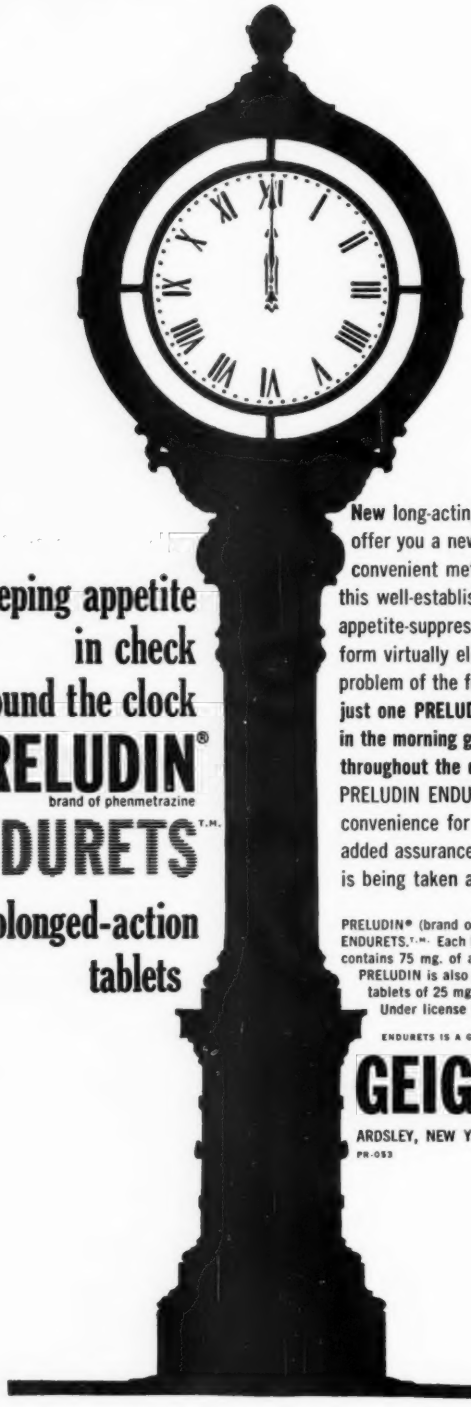

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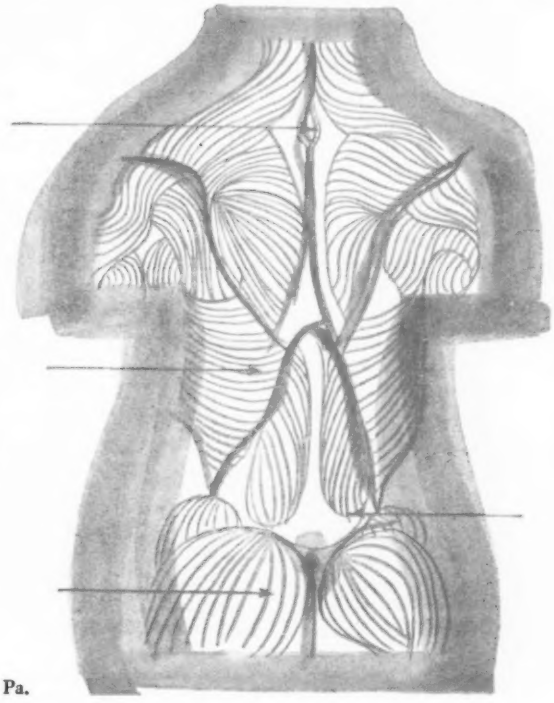

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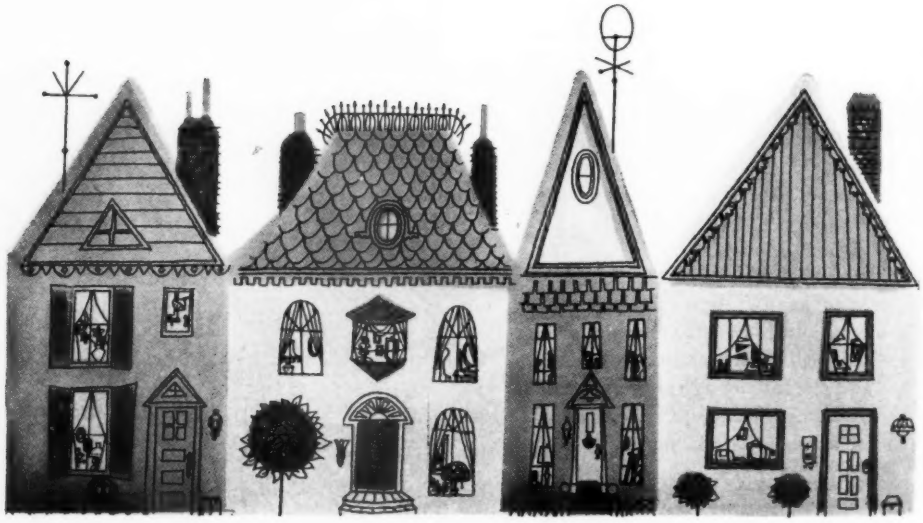

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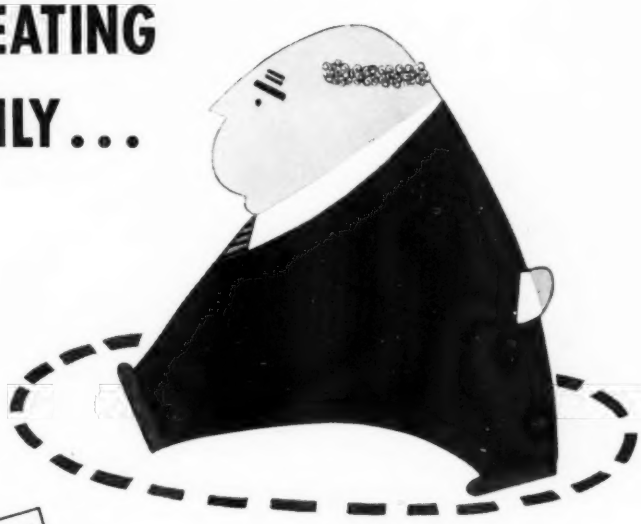

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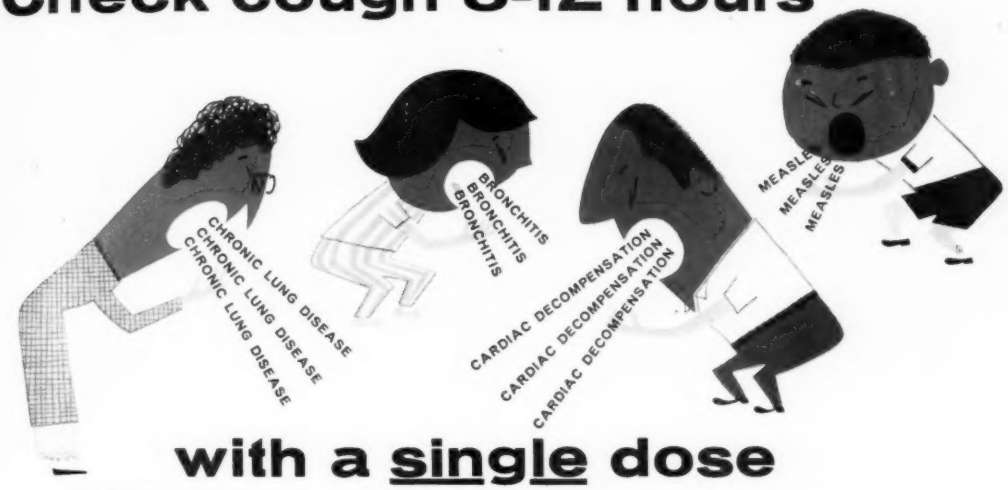

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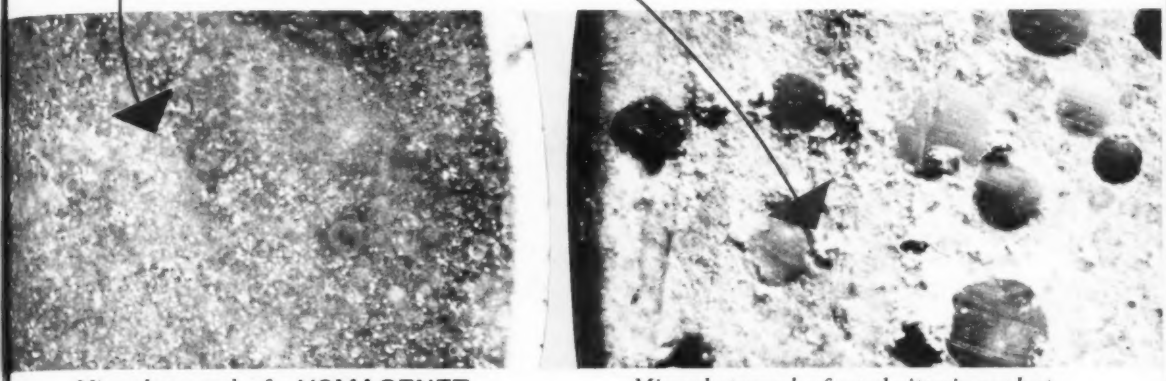

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1. Lewis, J.M., et al.: J. Pediatrics, *31*:496

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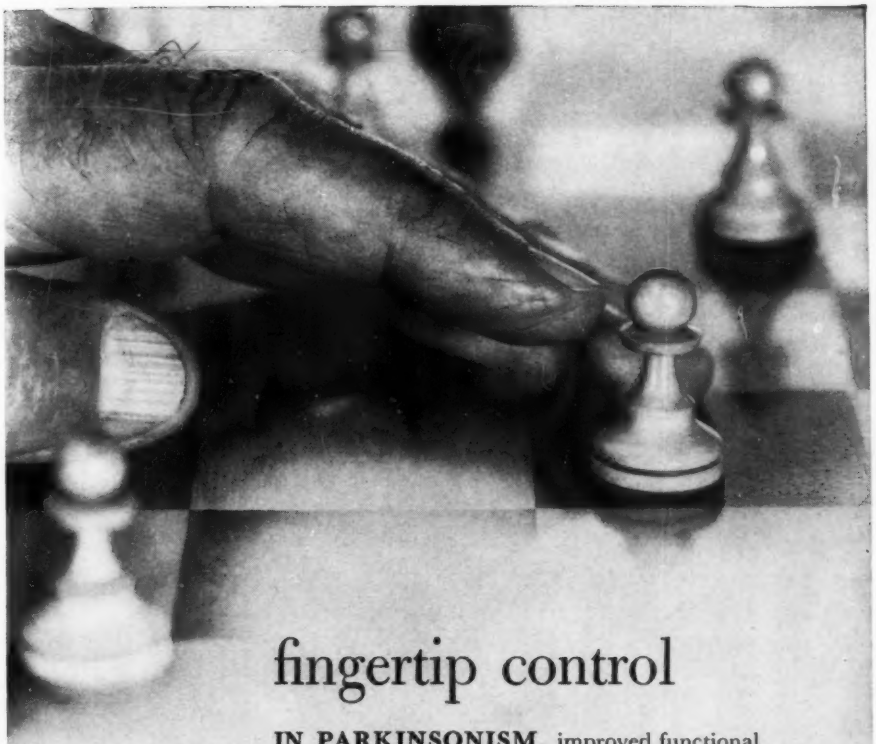

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1. Doshay, L. J. et al. J.A.M.A. 160:348 (Feb.) 1956.
2. Berris, H.: T. Lancet 74:245 (July) 1954.

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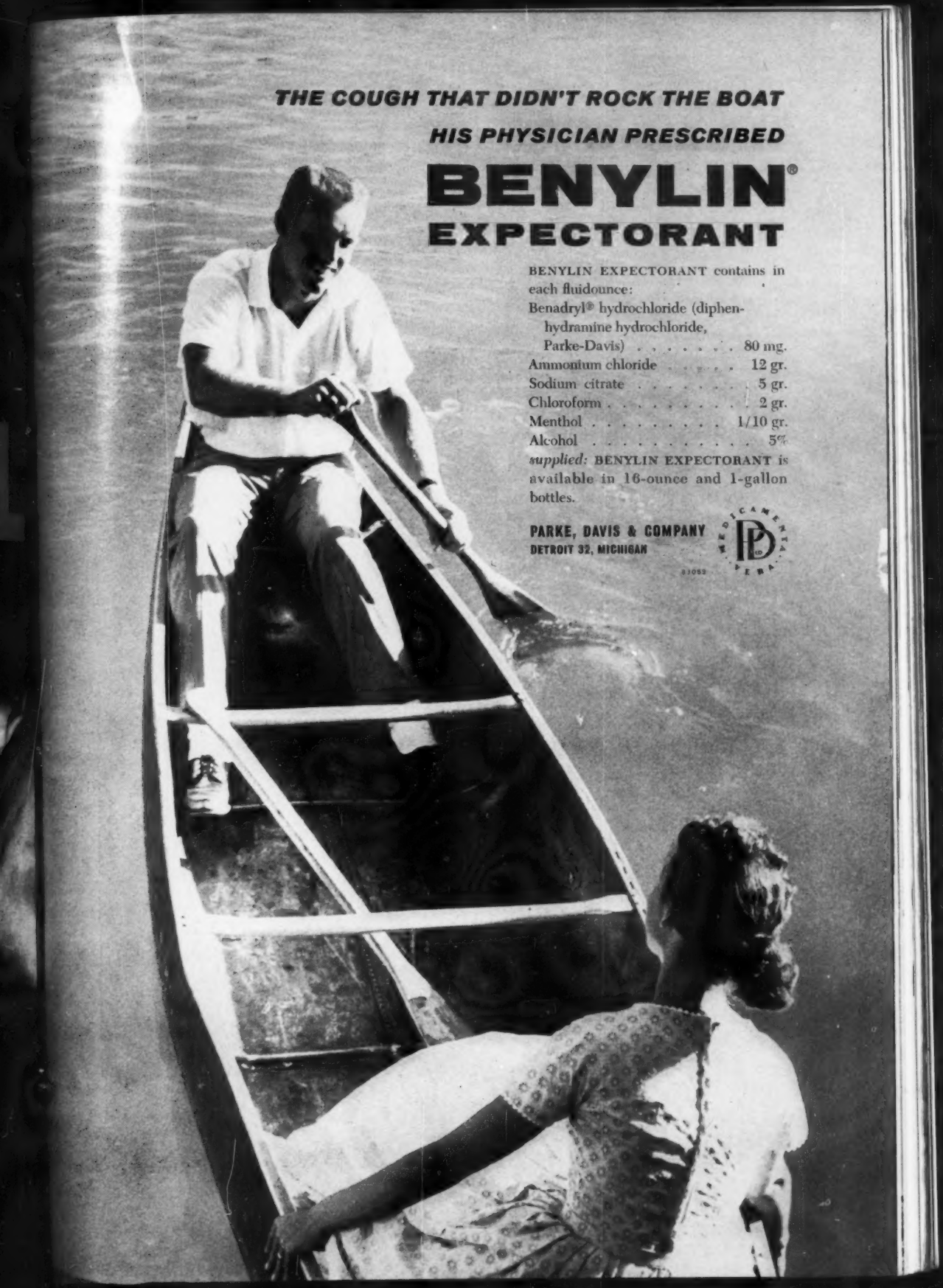
1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.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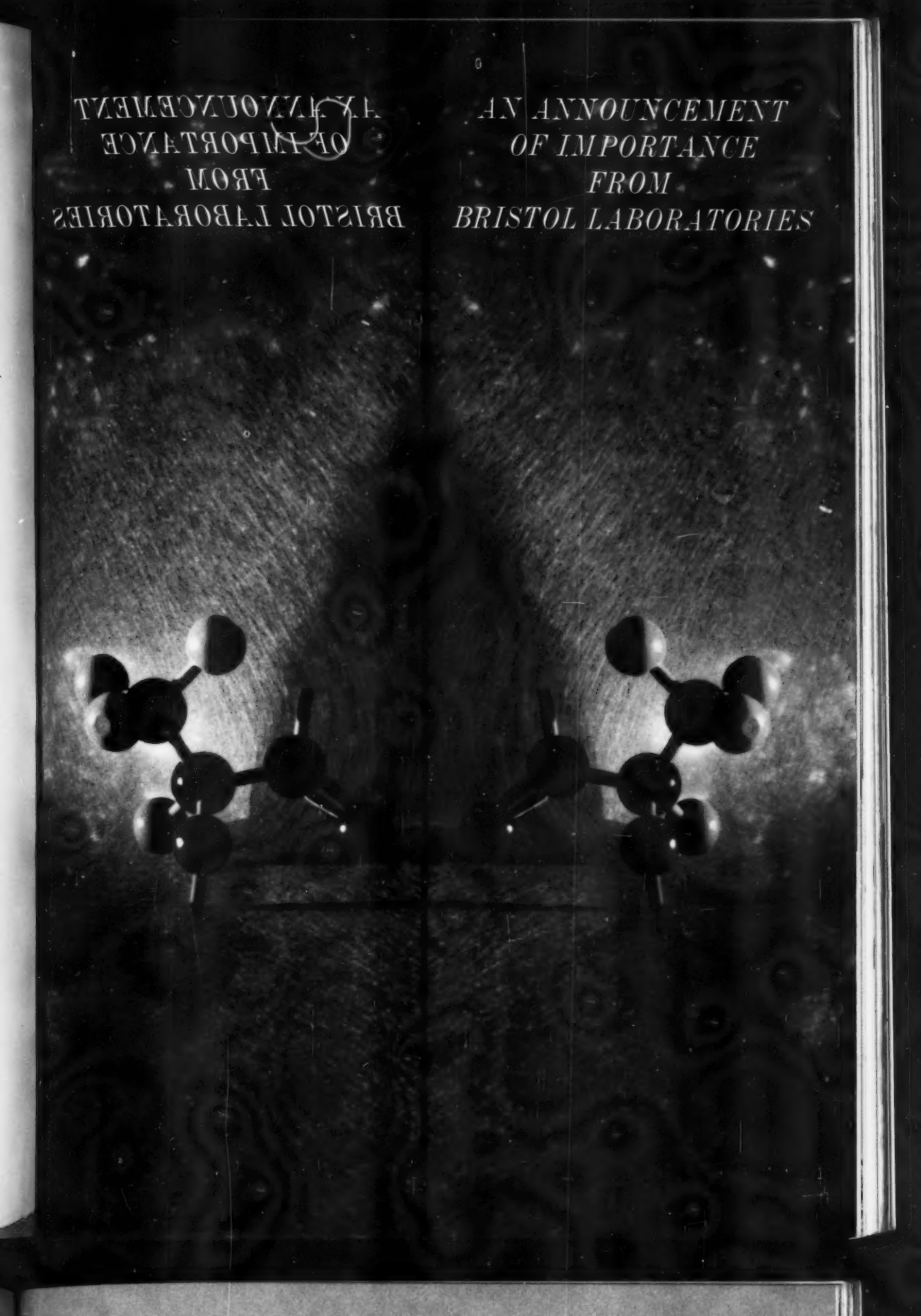

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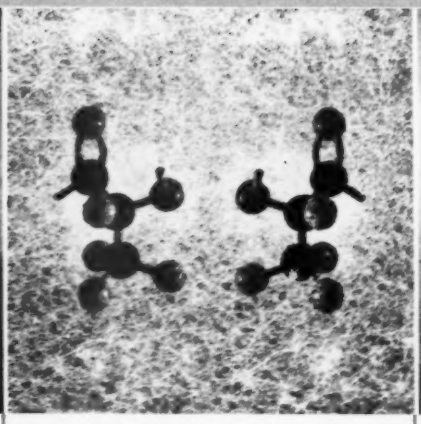

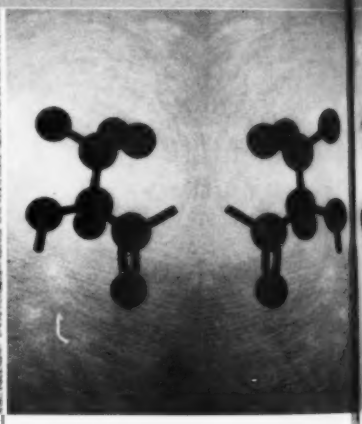

BLOOD LEVELS TWICE AS HIGH AS WITH POTASSIUM PENICILLIN V

SAFER ORAL ROUTE PROVIDES HIGHER BLOOD LEVELS THAN INTRAMUSCULAR PENICILLIN G

IMPROVED ANTIBIOTIC EFFECT FROM COMPLEMENTARY ACTION OF ISOMERS

TIC ADVANTAGES ACCOMPANY MOLECULAR ASYMMETRY

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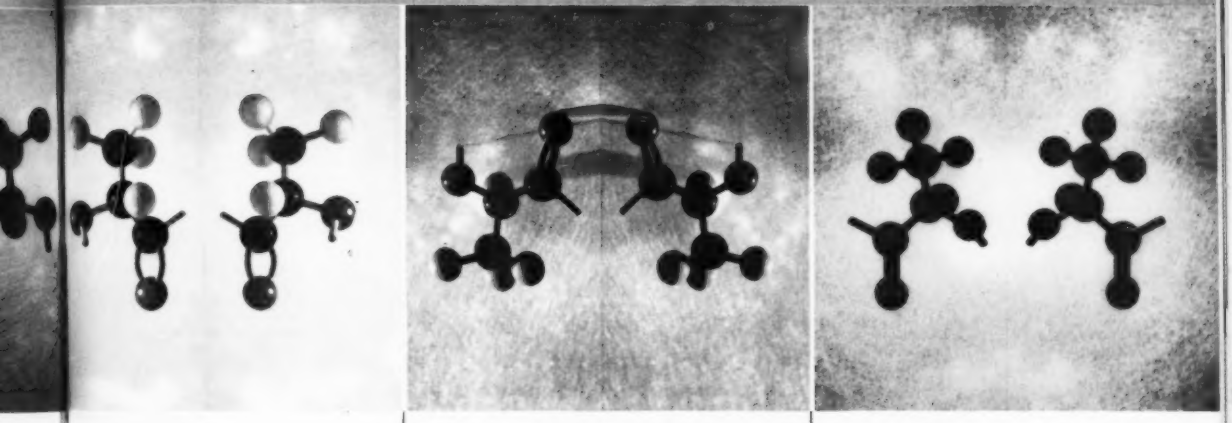


ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSE

REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE

MANY STAPH STRAINS MORE SENSITIVE TO SYNCILLIN

BRISTOL

ORIGIN OF A NEW SYNTHETIC PENICILLIN

In March, 1957, Dr. John C. Sheehan of the Massachusetts Institute of Technology announced the total synthesis of penicillin from common raw materials, thus solving a problem which had baffled research workers for more than 15 years. Although total synthesis was not commercially practicable, this work, sponsored by Bristol Laboratories, made possible the subsequent synthesis of new penicillins not occurring in nature. Later scientists at Beecham Laboratories in England discovered that a key intermediate (6-aminopenicillanic acid) could be produced by a fermentation process. With these achievements, large scale production of synthetic penicillins became feasible.

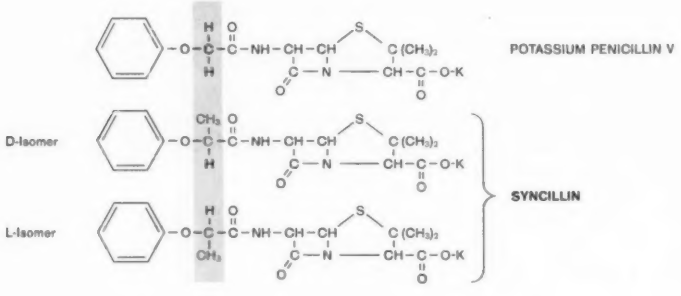
Organic chemists at Bristol then embarked upon an intensive program to develop better penicillins. Over five hundred were synthesized and underwent preliminary screening. Forty-six showed sufficient promise to warrant further investigation. Extensive microbiological, pharmacological, and clinical screening indicated that one compound, SYNCILLIN, had advantages of major importance over other penicillins.

SYNCILLIN is the N-acylation product of 6-aminopenicillanic acid and α-phenoxypropionic acid (the phenylether of lactic acid). It is freely soluble in water and remarkably resistant to decomposition by acid. The acid stability of SYNCILLIN is equivalent to that of penicillin V at pH 2 and pH 3 at 37° C.[1]

SIGNIFICANCE OF MOLECULAR ASYMMETRY AND ISOMERIC COMPLEMENTARITY

SYNCILLIN has a molecular configuration similar to penicillin V, but contains an additional CH_3 group so positioned as to render the adjacent carbon atom asymmetric. (In the formulae below, the added CH_3 group is shown in blue and the asymmetric carbon atom in red.) As a result, SYNCILLIN occurs as a mixture of two isomers.

Each isomer has been synthesized in essentially pure form and found to possess distinctive chemical and biological properties. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. As produced, SYNCILLIN is a mixture of the L-isomer and the D-isomer. As will be shown later, the antibiotic effect of the clinically available mixture, SYNCILLIN, is greater than either isomer alone against many organisms. This phenomenon is referred to here as *isomeric complementarity*.



SYNCILLIN

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ISOMERIC COMPLEMENTARITY DEMONSTRATED IN VITRO

The *in vitro* minimum inhibitory concentration (MIC) of SYNCILLIN and of each of its two component isomers was determined for a variety of common pathogens and laboratory test organisms. As may be seen from Table 1, all three are highly effective against penicillin-susceptible staphylococci and against pneumococci, streptococci, gonococci, and corynebacteria; all are ineffective against Salmonella, *E. coli*, and other gram-negative coliform bacilli.

SYNCILLIN was more active against many of the test strains including some streptococci and staphylococci than either of its components. This demonstrates *in vitro* the phenomenon of isomeric complementarity.

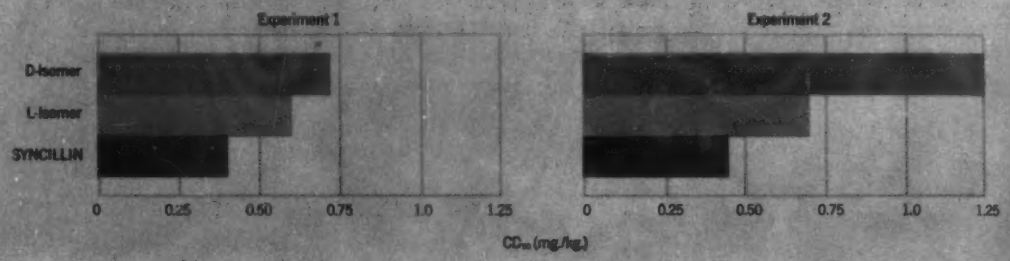
TABLE 1

Minimum Concentrations of SYNCILLIN and Components Required to Inhibit a Wide Range of Bacteria

ISOMERIC COMPLEMENTARITY CONFIRMED IN VIVO

To determine the median curative dose (CD_{50}) mice were infected with 100 times the lethal dose of *Staphylococcus aureus*. Each penicillin being tested was administered intramuscularly at the same time, and the dose required to cure half the animals determined. The greater effect of the mixture of the two isomers (SYNCILLIN) is shown in two independent experiments. (See Figure 1.) Note that isomeric complementarity is thus confirmed *in vivo*.

FIGURE 1 — Median Curative Dose (CD_{50}) for *Staphylococcus aureus* (var. Smith) Infections

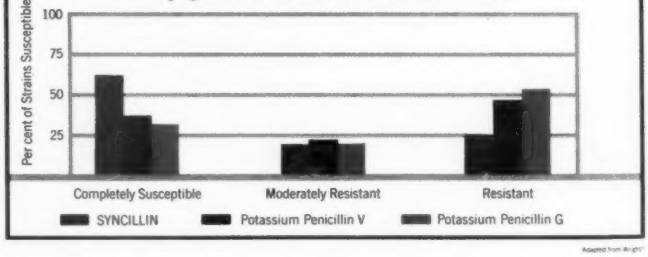


MANY STRAINS OF STAPHYLOCOCCI MORE SENSITIVE TO SYNCILLIN

SYNCILLIN has been tested against a large number of strains of *Staphylococcus aureus* isolated from clinical sources. Many organisms resistant to potassium penicillin G and potassium penicillin V proved sensitive to SYNCILLIN.

Wright[2] performed sensitivity studies on 54 strains, the majority of which were resistant or moderately resistant to penicillin V and penicillin G. Thirty-two (60%) of the strains were sensitive to SYNCILLIN, approximately twice as many as with the other penicillins. (See Figure 2.) In two-thirds of the isolates, SYNCILLIN produced inhibition at concentrations lower than those required for either of the other antibiotics. One strain was more sensitive to penicillin G.

FIGURE 2 – *In Vitro* Sensitivity of 54 Strains of Coagulase-Positive *Staphylococcus aureus* from Clinical Sources



Adapted from Wright[2]

SYNCILLIN

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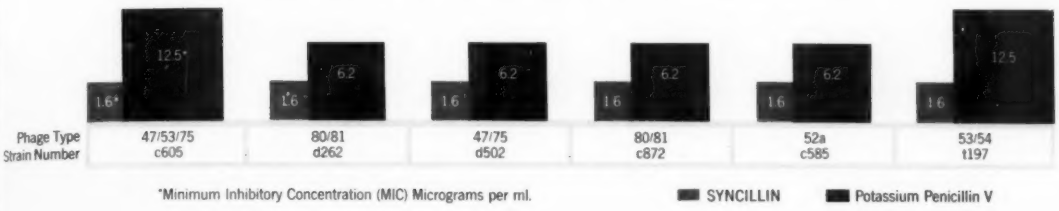
Of equal interest are the findings of White.[3] Six penicillin-resistant strains of staphylococci were isolated from hospital infections. None was sensitive to potassium penicillin V. All were sensitive to SYNCILLIN. (See Figure 3.)

FIGURE 3

Minimum Concentrations of SYNCILLIN Required to Inhibit
Hospital Strains of *Staphylococcus aureus* Resistant to Potassium Penicillin V

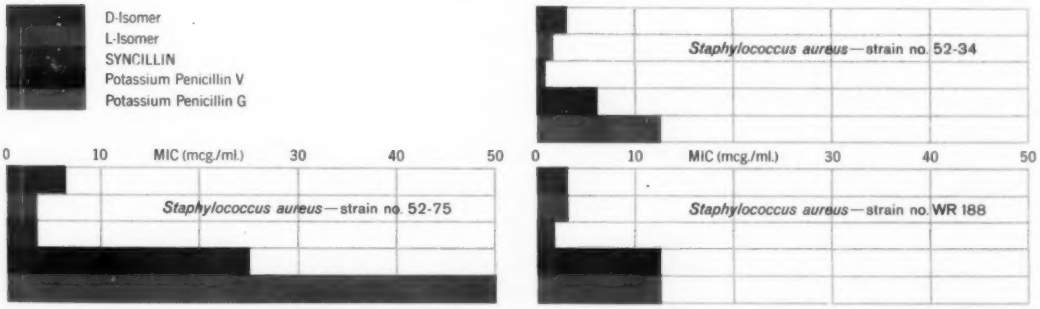


The efficacy of SYNCILLIN against the type 80/81 Staphylococcus (dangerous and widespread in hospitals) is worthy of special attention.

The complementary action of the component isomers is also seen with strains of staphylococci resistant to penicillins. Note that SYNCILLIN is more effective than either isomer against strains 52-34 and WR 188. (See Figure 4.) Against all three strains, SYNCILLIN is effective at concentrations below serum levels, while penicillins V and G are ineffective.

FIGURE 4

Minimum Inhibitory Concentrations (MIC) for Coagulase-Positive
Penicillin-Resistant Strains of *Staphylococcus aureus*



Isomeric complementarity has thus been demonstrated for:

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figure 1)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

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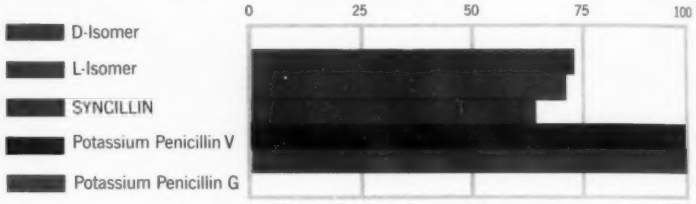
ISOMERIC COMPLEMENTARITY SHOWN BY REDUCED RATE OF INACTIVATION BY PENICILLINASE

Bacterial resistance to penicillin has been attributed to the action of penicillin-inactivating enzymes produced by the invading organisms.[4] As shown in Figure 5, SYNCILLIN is less affected by staphylococcal penicillinase than either of its component isomers – a further demonstration of isomeric complementarity. Further, SYNCILLIN is shown to be less inactivated by this enzyme than penicillin V and penicillin G. Resistance to SYNCILLIN develops in a slow, step-wise manner characteristic of other penicillins, in contrast to the usually rapid development of resistance to streptomycin.

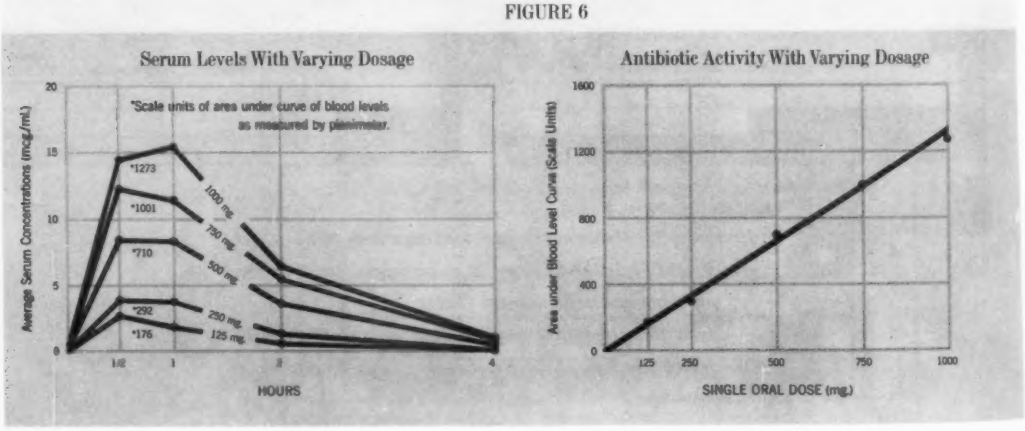
FIGURE 5—Effect of Staphylococcal Penicillinase on Different Penicillins



ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSAGE

Cronk[5] studied blood levels after administering varying amounts of SYNCILLIN. (Figure 6.) Total antibiotic activity (obtained by measuring areas under curves with a planimeter) increases rapidly as the dose is doubled. These data show that increased dosage markedly increases serum concentration and thus may enhance the drug's effectiveness.

FIGURE 6



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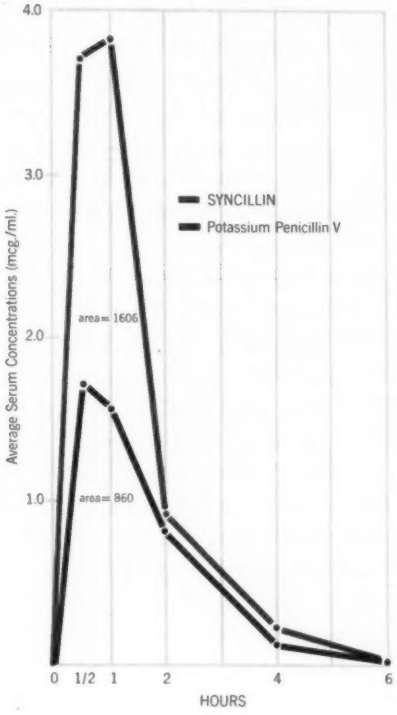
BLOOD LEVELS TWICE AS HIGH AS WITH POTASSIUM PENICILLIN V AFTER ORAL ADMINISTRATION

Wright[6] performed comparative crossover blood level studies on volunteer subjects receiving equivalent amounts of potassium penicillin V and SYNCILLIN. The peak concentrations attained during the first hour after administration were twice as high with SYNCILLIN.

The total antibiotic activity as measured by the area under the curves (see Figure 7) indicates an almost 2 to 1 superiority of SYNCILLIN (1606) over potassium penicillin V (860).

The higher blood levels may be of value with organisms of only moderate penicillin-sensitivity where doubling the blood concentration may be essential for effective bactericidal action. In addition these higher levels may be necessary where there is infection in areas with a poor blood supply.[7] Under these circumstances a higher blood concentration may provide the increased diffusion pressure required to deliver adequate amounts to the tissue.

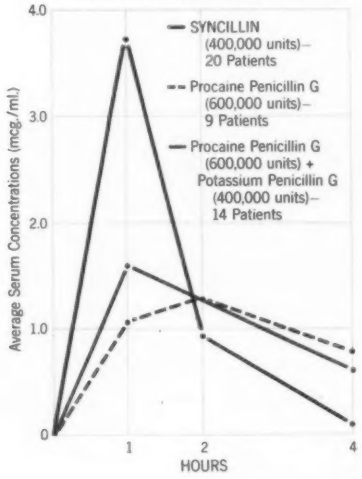
FIGURE 7
20 Subject Crossover
250 mg. Single Dose

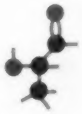


BLOOD LEVELS MUCH HIGHER THAN WITH INTRAMUSCULAR PENICILLIN G

In addition, blood levels attained with oral SYNCILLIN[6] are much higher than those with intramuscular penicillin G.[8a,b] (See Figure 8.) Note that the level at one hour for SYNCILLIN (3.8 mcg./ml.) is more than twice as high as with procaine penicillin G, even when reinforced with potassium penicillin G (1.6 mcg./ml.). Since penicillins are *bactericidal*, these intermittent high serum levels can be clinically significant. Thus, SYNCILLIN offers the promise of superior efficacy via the safer oral route.

FIGURE 8—Serum Levels after Oral Administration of SYNCILLIN (250 mg.) and after Intramuscular Injection of Penicillin G





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REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE

SYNCILLIN has been administered in multiple doses to 437 patients and volunteers. One patient developed itching during therapy, possibly an allergic side effect. Another had a purpuric rash, but no relationship to SYNCILLIN was established. No reactions were observed in 9 patients with a known history of sensitivity to penicillin.

While the above data suggests the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *The usual precautions for oral penicillin therapy should be observed.* Patients with histories of asthma, hay fever, urticaria, or previous penicillin-sensitivity should especially be watched carefully. Since SYNCILLIN is administered orally, it may be expected to be safer than parenteral penicillin.

As Flippin[9] recently stated, "... it is well established that serious allergy to the drug [penicillin] is most likely to occur following parenteral administration, especially after repeated intramuscular injections; the oral route is least likely to initiate severe hypersensitivity reactions. This can be explained partly by the fact that when reactions develop following oral medication, they are usually slow enough to treat symptomatically; thus the progression of the reaction can usually be interrupted.... In view of the relatively high incidence of severe allergy to injectable penicillin, it would seem advisable to employ oral penicillin routinely, except in the control of infections involving the blood stream, endocardium, meninges, etc., in which cases the parenteral route remains the preferred treatment."

SYNCILLIN, like other penicillins, is essentially free of other toxicity. No hematopoietic, hepatic, or renal toxicity was observed in 210 volunteers receiving 1 gm. daily for 2 to 3 weeks.[10]

CLINICAL EFFICACY DEMONSTRATED IN PENICILLIN-SENSITIVE INFECTIONS

Clinical trials conducted by Blau and Kanof,[11] White,[12] Prigot,[13] Robinson,[14] Dube,[15] Ferguson,[16] Rutenburg,[17] Richardson,[18] Bunn,[19] Cronk,[5] Kligman,[10] and Yow [20] demonstrated the efficacy of SYNCILLIN in a variety of streptococcal, staphylococcal, pneumococcal, and gonococcal infections. Conditions treated included respiratory, skin, soft tissue, wound, and chronic urinary tract infections; acute gonorrhea; cellulitis; septicemia; otitis media; gingivitis; and Vincent's angina. In a few patients SYNCILLIN was used for rheumatic fever or gonorrheal prophylaxis.

One hundred seventy-two of one hundred ninety-six patients responded favorably to SYNCILLIN. The failures included 1 patient with pustular dermatoses, 10 elderly patients with chronic urinary tract infections, 1 patient with gonorrhea, 1 patient with a gram-negative infection, and 10 patients with staphylococcal infections. Lack of response of staphylococcal infections was attributed to the presence of resistant organisms or local suppurative foci requiring drainage.

SYNCILLIN

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Relatively few side effects were encountered. One patient experienced moderate itching of the skin which was controlled by an antihistamine. Another reported pruritus ani which did not interfere with therapy. Diarrhea occurred in 4 instances. There was one purpuric rash, but no relationship to SYNCILLIN could be established.

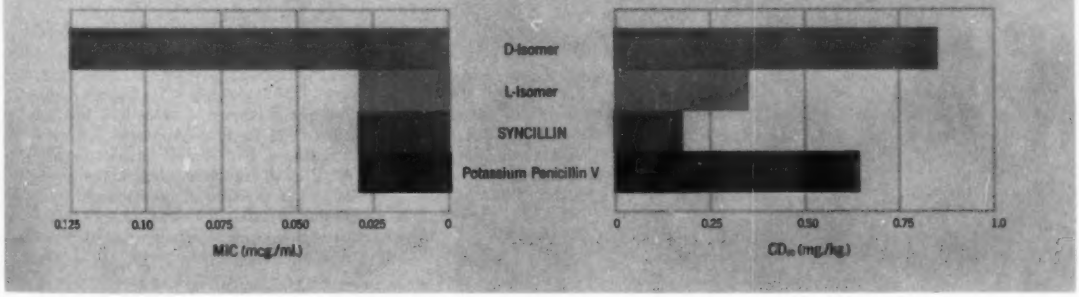
Clinical response usually begins within 24 hours in infections susceptible to SYNCILLIN. Recovery occurs in 4 to 7 days depending upon the severity of the infection. Gonorrheal infections respond very promptly to SYNCILLIN; 500 mg. b.i.d. for two days usually produce bacteriologic cures.

IMPROVED ANTIBIOTIC EFFECT FROM COMPLEMENTARY ACTION OF ISOMERS

SYNCILLIN is a mixture of isomers. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. Furthermore, the D- and L-isomers have other distinguishing chemical, pharmacological, and microbiological properties. Their *in vivo* and *in vitro* activities differ for many important pathogens. *Against many of the organisms tested, the combination of isomers* (SYNCILLIN) *is much more active than the stronger isomer alone.* This phenomenon of isomeric complementarity is not always demonstrable, for in a few instances SYNCILLIN is slightly less active.

Isomeric complementarity has previously been demonstrated *in vitro* (Figure 4) and *in vivo* (Figure 1). Figure 9 reveals a third form of superiority related to isomeric complementarity. Equal concentrations of SYNCILLIN and penicillin V were required to inhibit this growth of staphylococci *in vitro*. But, *in vivo*, a much smaller amount of SYNCILLIN *(one-third that of penicillin V)* was effective in an experimental infection with the same strain. These observations on complementary action indicated the advantage of producing the mixture of isomers as the medication to be made available for clinical therapy.

FIGURE 9 — Comparison of CD_m and MIC Values Against *Staphylococcus aureus* (var. Smith)



Isomeric complementarity has thus been demonstrated for:

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figures 1 and 9)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

— *staphylococcal penicillinase antibiotic inactivation (Figure 5)*

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Indications:

SYNCILLIN is recommended in the treatment of infections caused by pneumococci, streptococci, gonococci, corynebacteria, and penicillin-sensitive staphylococci. In addition, SYNCILLIN is effective against certain strains of staphylococci resistant to other penicillins.

SYNCILLIN, like other oral penicillins, is not recommended at the present time in deep-seated or chronic infections, subacute bacterial endocarditis, meningitis, or syphilis.

Dosage:

125 mg. or 250 mg. three times daily, depending on the severity of infection. Larger doses (e.g., 500 mg. t.i.d.) may be used for more severe infections. SYNCILLIN may be administered without regard to meals.

Beta hemolytic streptococcal infections should be treated with SYNCILLIN for at least ten days.

Precautions:

While present data suggest the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *Therefore the usual precautions with oral penicillin therapy must be observed.* Patients with histories of asthma, hay fever, urticaria, or previous reactions to penicillin should be watched with special care.

Diarrhea has been reported occasionally following heavy dosage. If this occurs, the interval between dosages should be lengthened.

If superinfection occurs during therapy, appropriate measures should be taken.

Since some strains of staphylococci are resistant to SYNCILLIN as well as to other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment. As is true with all antibiotics, clinical response does not always correlate with laboratory bacterial sensitivity reports.

Supply:

125 and 250 mg. tablets, bottles of 25 and 100. 125 mg. powder for oral solution, 60 ml. vials.

References: 1. Lein, J.: Microbiology report to Bristol Laboratories Inc. 2. Wright, W. W.: Microbiology report to Bristol Laboratories Inc. 3. White, A. C.: Microbiology report to Bristol Laboratories Inc. 4. Dubos, R. J.: Bacterial and Mycotic Infections of Man, 3rd edition, Philadelphia, J. B. Lippincott Co., p. 690. 5. Cronk, G. A.: Clinical report to Bristol Laboratories Inc. 6. Wright, W. W.: Clinical report to Bristol Laboratories Inc. 7. Kass, E. H.: Am. J. Med. *18*:764 (May) 1955. 8a. White, A. C.; Couch, R. A.; Foster, F.; Calloway, J.; Hunter, W., and Knight, V.: in Welch, H. and Marti-Ibañez, F.: Antibiotics Annual — 1955-1956, Medical Encyclopedia, Inc., New York, 1956, p. 490. b. Data on file — at Bristol Laboratories. 9. Flippin, H. F.: Pennsylvania M. J. *62*:864 (June) 1959. 10. Kligman, A.: Clinical report to Bristol Laboratories Inc. 11. Blau, S., and Kanof, N.: Clinical report to Bristol Laboratories Inc. 12. White, A. C.: Clinical report to Bristol Laboratories Inc. 13. Prigot, A.: Clinical report to Bristol Laboratories Inc. 14. Robinson, C.: Clinical report to Bristol Laboratories Inc. 15. Dube, A. H.: Clinical report to Bristol Laboratories Inc. 16. Ferguson, B.: Clinical report to Bristol Laboratories Inc. 17. Rutenburg, A. M.: Clinical report to Bristol Laboratories Inc. 18. Richardson, J. H.: Clinical report to Bristol Laboratories Inc. 19. Bunn, P. A.: Clinical report to Bristol Laboratories Inc. 20. Yow, E. M.: Clinical report to Bristol Laboratories Inc.

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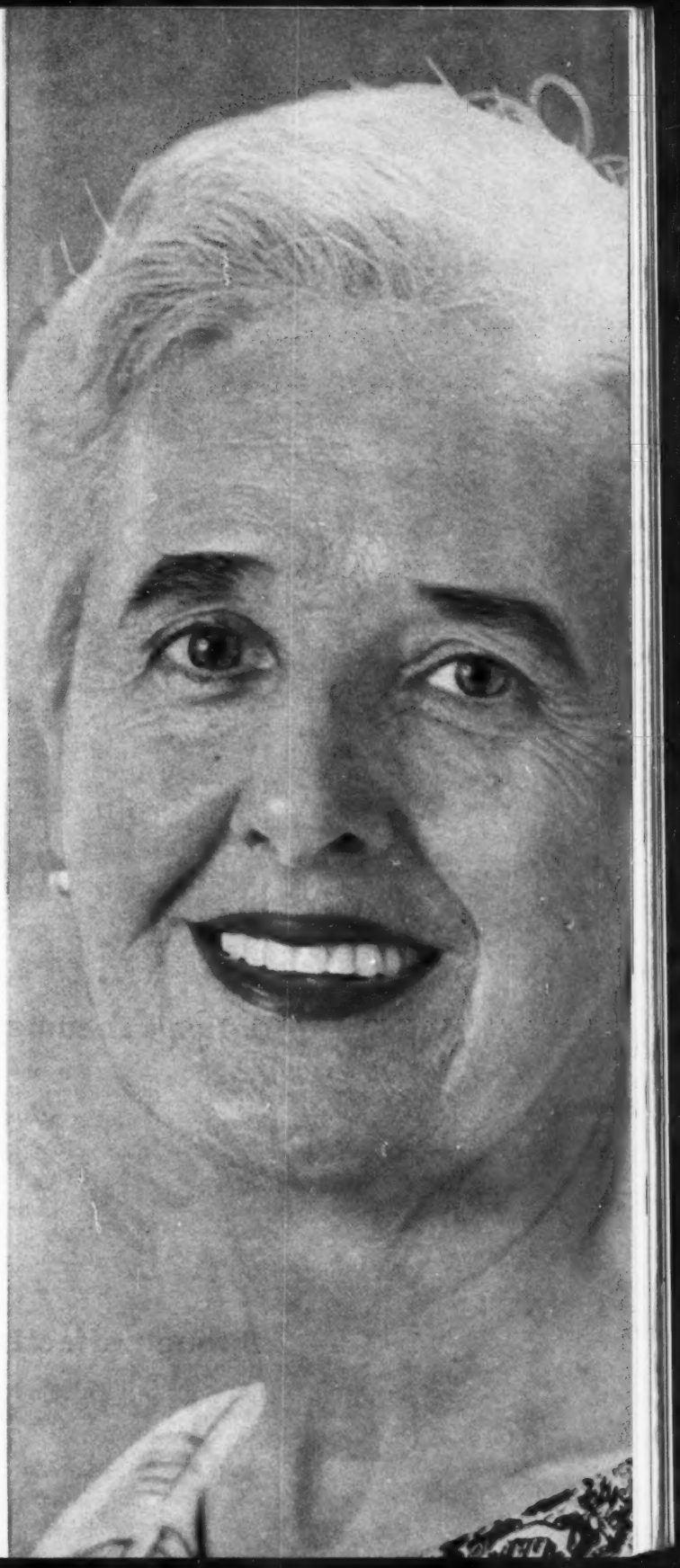

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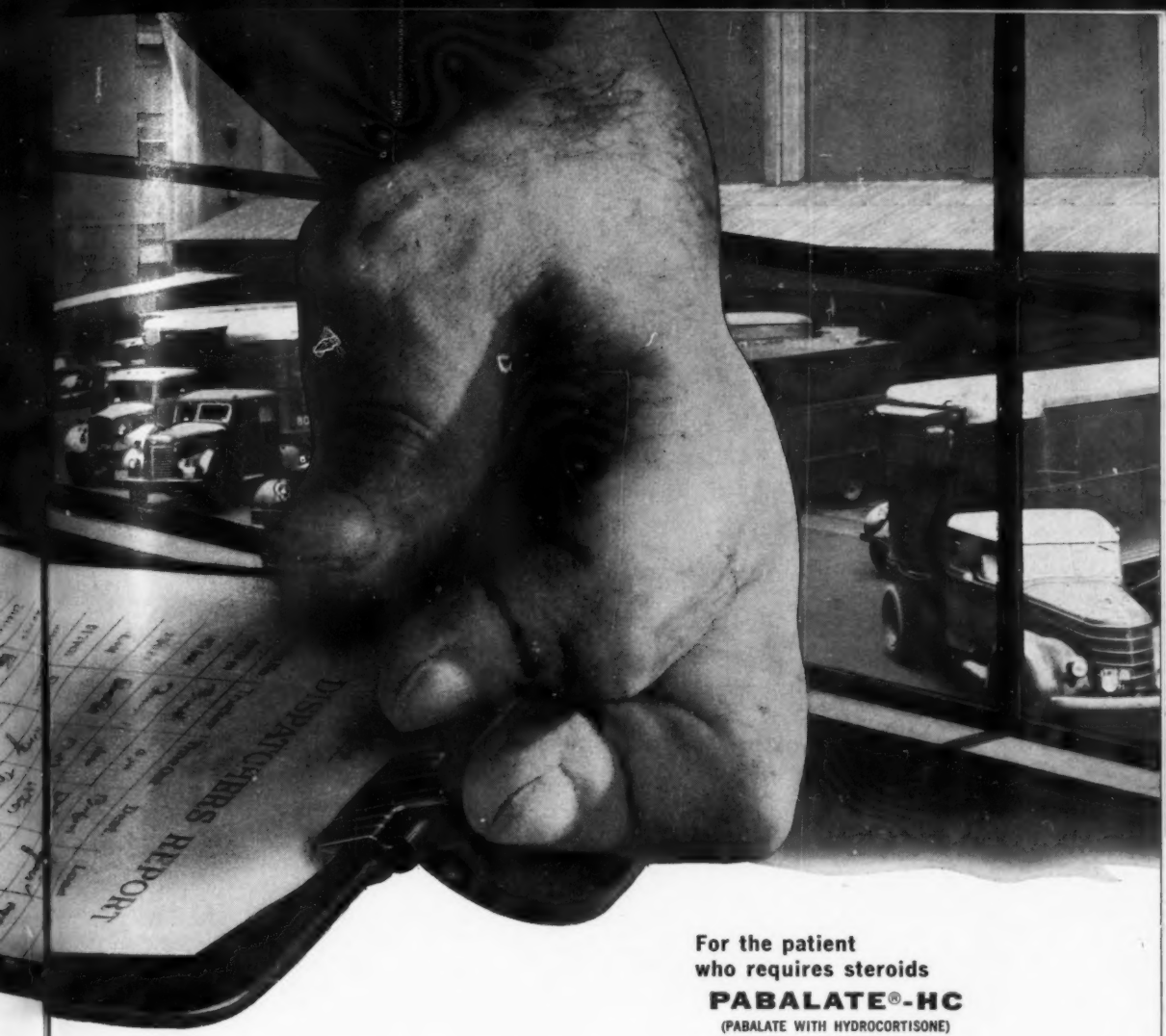

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Ascorbic acid	50.0 mg.

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PABALATE® - Sodium Free

Pabalate, with sodium salts replaced by potassium salts.

In each enteric-coated tablet:

Potassium salicylate	0.3 Gm. (5 gr.)
Potassium para-aminobenzoate	0.3 Gm. (5 gr.)
Ascorbic acid	50.0 mg.

For the patient who requires steroids

PABALATE®-HC

(PABALATE WITH HYDROCORTISONE)

Comprehensive synergistic combination of steroid and nonsteroid antirheumatics... full hormone effects on low hormone dosage . . . satisfactory remission of rheumatic symptoms in 85% of patients tested.

In each enteric-coated tablet:

Hydrocortisone (alcohol)	2.5 mg.
Potassium salicylate	0.3 Gm.
Potassium para-aminobenzoate	0.3 Gm.
Ascorbic acid	50.0 mg.

PABALATE® Robins PABALATE®-HC

For steroid or non-steroid therapy: SAFE DEPENDABLE ECONOMICAL

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Atopic dermatitis before treatment

NOW...
to relieve inflammation fast

- mg. for mg. the most active steroid topically—up to 40 times the potency of hydrocortisone
- optimal not minimal steroid concentration for peak effectiveness . . . maximal contact at the site of the lesion
- stops the itch-scratch cycle to aid inflammation relief and maintain patient comfort day and night
- quick-acting broad antimicrobial activity when infection threatens recovery
- no irritating steroid particles, no sting, stain, smell, stickiness

After treatment ACTUAL CLINICAL PHOTOGRAPHS

TOPICAL CREAM

NeoDecadron*

DEXAMETHASONE 21-PHOSPHATE—NEOMYCIN SULFATE

ICATIONS: Allergic or inflammatory dermatoses, with or hout pruritus; sunburn; insect bites; otitis externa ly if the drum is intact).

TION: Steroids should not be used in the presence of berculosis of the skin.

AGE: A small quantity of NeoDECADRON Topical Cream 1%) is applied to the affected area 2-3 times daily.

tional information is available to physicians on request.

DECADRON and DECADRON are trademarks of Merck & Co., Inc.

Product	Steroid Concentration	ACTIVE INGREDIENTS: Dexamethasone 21-Phosphate (as disodium salt)	ACTIVE INGREDIENTS: Neomycin Sulfate	Supplied
NeoDECADRON Topical Cream	0.1%	1 mg./Gm.	5 mg./Gm. (equivalent to 3.5 mg. neomycin base)	5 Gm. (⅙ oz.) tube 15 Gm. (½ oz.) tube
DECADRON® Phosphate	0.1%	1 mg./Gm.	—	5 Gm. (⅙ oz.) tube 15 Gm. (½ oz.) tube

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INTRODUCING

RUBRAMIN PC

SQUIBB VITAMIN B_{12} U.S.P. INJECTION

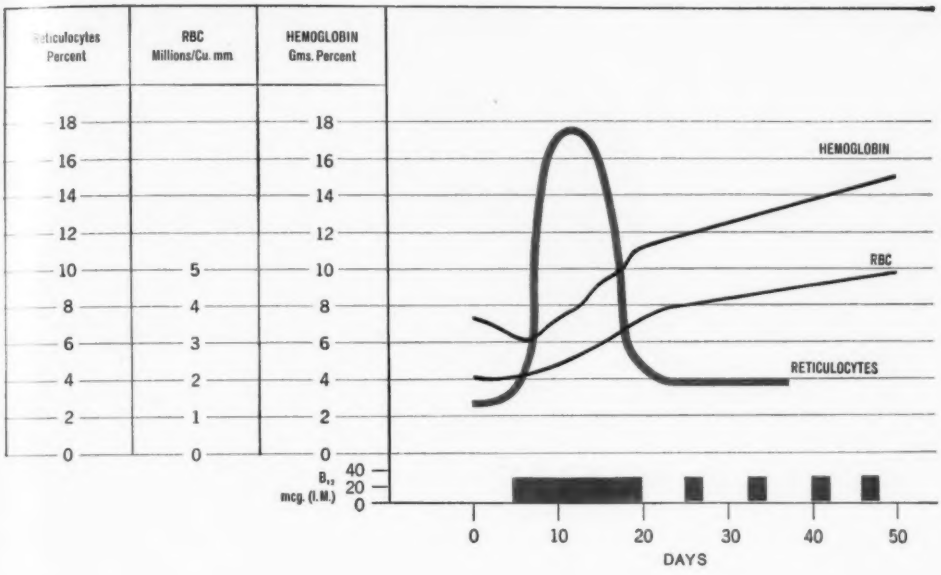
PURE CYANOCOBALAMIN INJECTION – CREATED AND PRODUCED BY SQUIBB – FOR THE MOST EXACTING STANDARDS OF INTRAVENOUS, INTRAMUSCULAR AND SUBCUTANEOUS ADMINISTRATION IN:

- *pernicious anemia*
- *severe nutritional macrocytic anemias*
- *severe nutritional neuropathies*
- *prevention of macrocytic anemia following partial or total gastrectomy*

and for the relief of pain in such conditions as:

trigeminal neuralgia; osteoarthritis; secondary burning paresthesias; herpes zoster; and neuroblastoma in children.

RUBRAMIN PC is highly effective whenever high doses of vitamin B_{12} are required.



TYPICAL HEMATOPOIETIC RESPONSE WHEN RUBRAMIN P C IS GIVEN INTRAMUSCULARLY TO A PATIENT WITH MEGALOBLASTIC ANEMIA *(schematic)*

highly potent and vital to metabolism

Vitamin B_{12} – one of the most potent biological factors known – is vital to basic metabolic functions, to normal formation of red blood cells and other formed elements of the blood, and to the functional integrity of myelinated fibers in the spinal cord and brain, as well as to the healthy condition of gastric and oral mucosa.

therapeutic agent of choice in pernicious anemia

Vitamin B_{12} is the therapeutic agent of choice in pernicious anemia, is effective in certain megaloblastic macrocytic anemias, and contributes to recovery or clinical improvement in a variety of neurological, liver and skin disorders.

non-toxic, remarkably free from side reactions

Despite its high level of activity, vitamin B_{12} is non-toxic and remarkably free from side reactions. It has been well-tolerated even when administered in massive doses.

potency confirmed by precise radioisotope measurement

The Radioisotope Tracer Method is now used routinely as an assay procedure in the production of RUBRAMIN, guaranteeing accurate label potency.

RUBRAMIN P C is now available in potencies for all your parenteral requirements: 30, 50 and 100 mcg. per cc., 10 cc. vials; 1000 mcg. per cc., 1 cc. and 10 cc. vials.

SQUIBB *Squibb Quality – the Priceless Ingredient*

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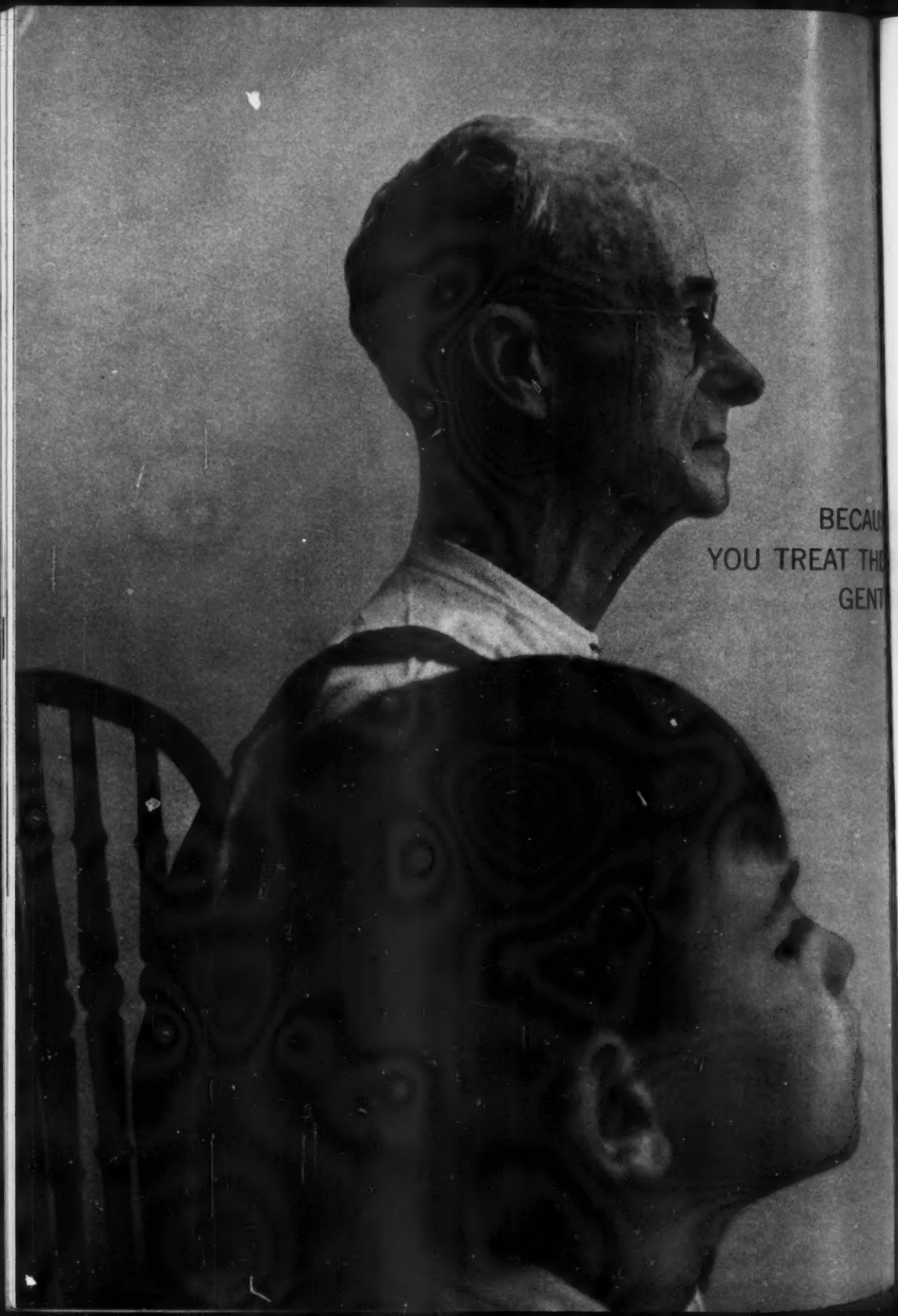
BECAU
YOU TREAT THI
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"In no case...
was there any rebound congestion."[1]

Your youngest patient as well as your oldest will find new Otrivin an unusually gentle yet remarkably effective nasal decongestant. Otrivin works quickly; its action is prolonged. Typical of many clinicians' reports is the one published by Kolodny[1]: Of 64 patients studied, 92 per cent had good or excellent results. "In no case studied was there any rebound congestion. Local side effects were minimal. . . . Extremely few systemic effects occurred. . . ."

NEW
OTRIVIN® FOR GENTLE RELIEF OF STUFFY NOSE
ON PRESCRIPTION ONLY

Otrivin is safe even for the very young. "The particularly striking feature of Otrivin solution was the absence of side effects, even in infants as young as two weeks."[2] "It is effective in low concentrations and is a safe nasal vasoconstrictor for even the young patient."[3]

SUPPLIED: Otrivin *Nasal Solution*, 0.1%; dropper bottles of 1 ounce. Otrivin *Nasal Spray*, 0.1%; plastic squeeze tubes of 15 ml. Otrivin *Pediatric Nasal Spray*, 0.05%; plastic squeeze tubes of 15 ml.

REFERENCES: 1. Kolodny, A. L.: Antibiotic Med. *6*:452 (Aug.) 1959. 2. Davis, M. R.: To be published. 3. Peluse, S.: In press.

Otrivin® hydrochloride (xylometazoline hydrochloride CIBA) 9/5795MK

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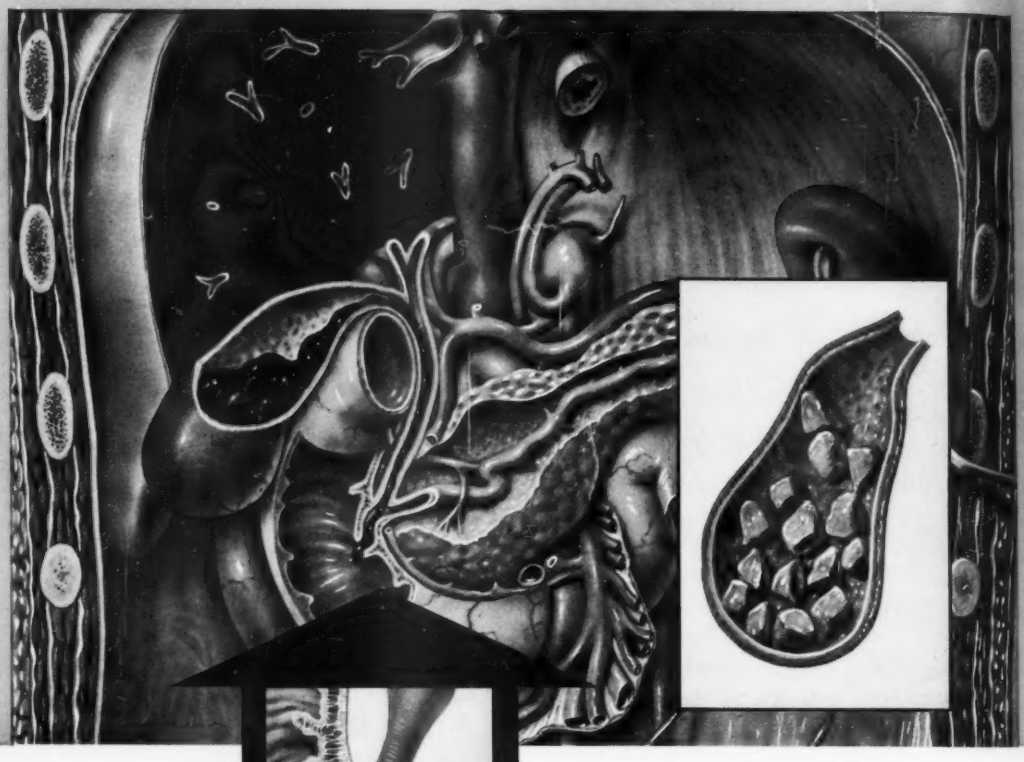

1. *Sphincter of Boyden*
2. *Sphincter of Oddi in Spasm*

BILIARY STASIS
constipation — nausea — dyspepsia
flatulence and eructation

The primary function of the Cholan preparations is to induce hydrocholeretic action. The active ingredient is the pure oxidized bile acid, dehydrocholic acid, Maltbie. The Cholans increase the volume of low viscosity bile flow to flush out the biliary tract. In addition, there is a suitable Cholan dosage form to provide symptomatic and physiologic relief of biliary stasis, spasm or emotional factors that cause or complicate digestive disturbance, hepato-biliary dysfunction, constipation of biliary origin, cholecystitis, cholangitis, or postoperative treatment.

Cholan DH® — hydrocholeretic action increases the flow and heightens the pressure of low viscosity bile for normal flushing of the biliary tract. In fact, Cholan DH will increase the volume of bile by 33% to 100%.

Cholan V (hydrocholeretic-spasmolytic) — the volume and pressure of thin bile flow in the biliary tract is increased, and the V mg. of homatropine methylbromide relax the gallbladder and biliary sphincters in severe and chronic spasm.

Cholan HMB — a combination for the increased flow of thin bile, smooth muscle relaxation for the gallbladder and biliary sphincters, and mild sedation for patients with hepato-biliary dysfunction further complicated by emotional factors.

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Sphincter Muscles in Normal Relaxation

Cholan DH®
Cholan V
Cholan HMB

With **Cholan** *therapy, the distressing symptoms of constipation, nausea, dyspepsia, flatulence and eructation disappear. Normal digestive function is quickly restored.*

Cholan DH® – dehydrocholic acid, Maltbie, 250 mg., a chemically pure oxidized bile acid. Dosage: 1 or 2 tablets t.i.d. after meals. **Cholan V** – dehydrocholic acid, Maltbie, 250 mg., and 5 mg. homatropine methylbromide. Dosage: 1 or 2 tablets t.i.d. after meals. **Cholan HMB** – dehydrocholic acid, Maltbie, 250 mg., 2.5 mg. homatropine methylbromide, and 8 mg. phenobarbital. Dosage: 1 or 2 tablets t.i.d. after meals.

Supplied: Bottles of 100, 500 and 1,000 tablets.

For a trial supply write to Professional Service Department

Maltbie

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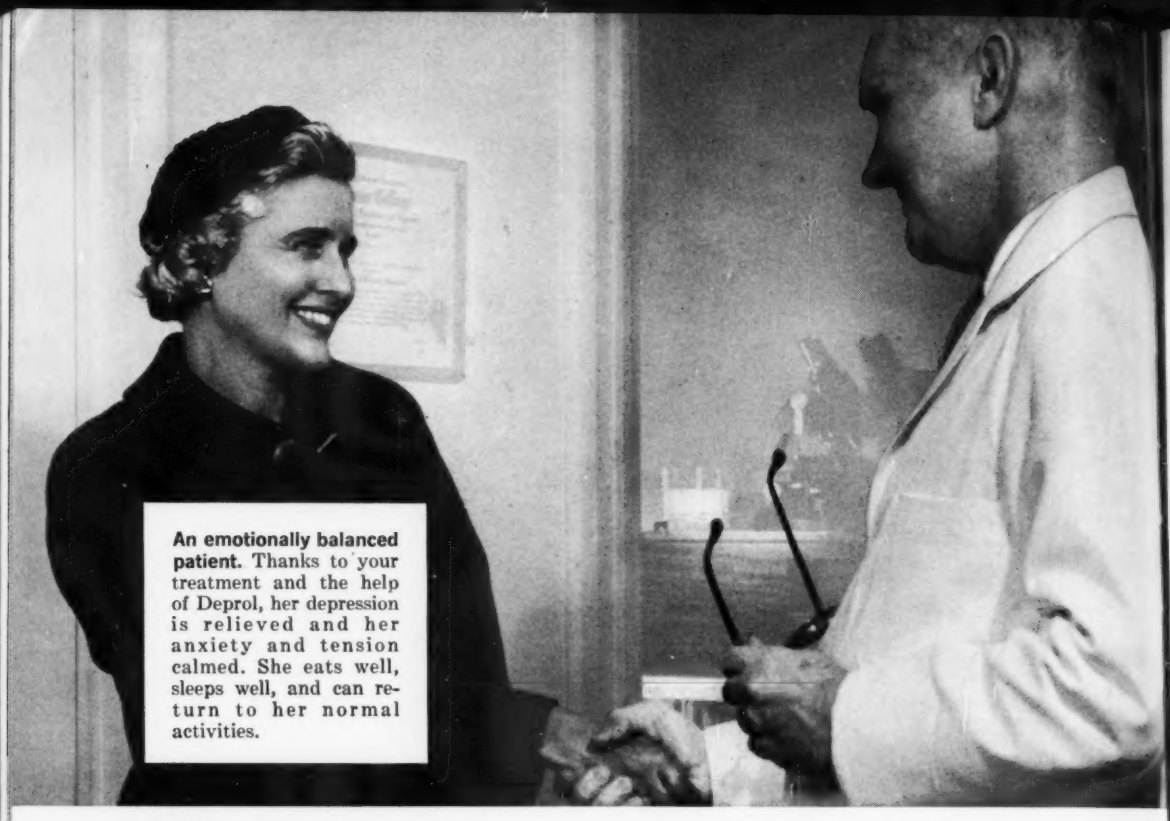


An emotionally balanced patient. Thanks to your treatment and the help of Deprol, her depression is relieved and her anxiety and tension calmed. She eats well, sleeps well, and can return to her normal activities.

Lifts depression...as it calms anxiety!

Deprol helps balance the mood by lifting depression as it calms related anxiety

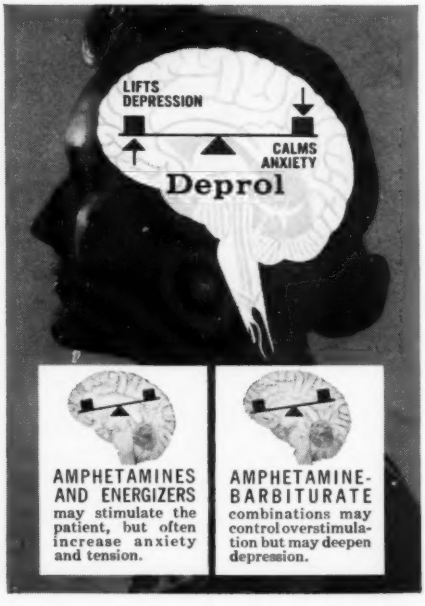
No "seesaw" effect of amphetamine-barbiturates and energizers

While amphetamines and energizers may stimulate the patient—*they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation—*they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety—both at the same time.

Safer choice of medication than untested drugs

Deprol does not produce hypotension, liver damage, psychotic reactions or changes in sexual function.



▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

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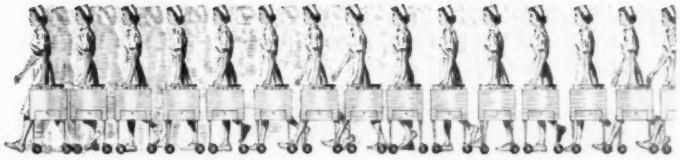
CD-473



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with 2 recording speeds • 3 sensitivities • provision for recording other waveforms • provision for visual monitoring

Almost without effort, this modern functional electrocardiograph can be wheeled noiselessly from room to room . . . around beds . . . into and out of elevators. Here are all the diagnostic advantages of the new Model 100 Viso-Cardiette electrocardiograph in a mobile console cabinet of hand-rubbed mahogany or rugged stain-proof light beige plastic laminate. Electrodes, Redux paste and all accessories — and the built-in automatic-retracting power cord — stay with the 100M Mobile Viso. For hospital, clinic or office use, this newest Sanborn electrocardiograph offers the ultimate in diagnostic usefulness and operating convenience. Model 100M Mobile Viso, $895 delivered, continental U.S.A.

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Model 300 Visette — only 18 pounds *complete*, briefcase size. You or your nurse can carry this truly portable instrument *anywhere* . . . ideal for "on-call" ECG work. Price $625 delivered, continental U.S.A.

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For topical infections, choose a 'B. W. & Co.'® 'SPORIN'...

'CORTISPORIN'®
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Combines the anti-inflammatory effect of hydrocortisone with the comprehensive bactericidal action of the antibiotics.

Each gram contains:
'Aerosporin'® brand Polymyxin B Sulfate 5,000 Units
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Offers combined antibiotic action for treating conditions due to susceptible organisms amenable to local medication.

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cushioned comfort—

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new RAMSES BENDEX Diaphragm

The cushioned comfort and sensitivity built into both the regular RAMSES® Diaphragm and the new RAMSES BENDEX,® a bow-bend Diaphragm, contribute to the physical ease and emotional security that encourage patient cooperation.

The regular RAMSES Diaphragm, suitable for most women, is distinguished by a soft cushioned rim and flexibility in all planes to permit complete freedom of motion. The complete unit —the new RAMSES "TUK-A-WAY"® Kit #701 with diaphragm, introducer and jelly, is attractively packaged in a new zippered case which opens top and side.

For those women who need a different type of diaphragm, the RAMSES BENDEX is now available, retaining all the desirable flexibility of RAMSES coil-spring construction. The bow-bend or arc-ing type of construction makes it especially suitable for the woman with structural abnormalities such as cystocele or rectocele. No introducer is required. Further information about the new BENDEX may be obtained from your local Schmid representative.

RAMSES Jelly,* uniquely suited for use with either type of RAMSES Diaphragm, further contributes to the patient's comfort and protection by flowing freely over the rim and surface to lubricate the diaphragm, aid in insertion, and protect the patient for *ten full hours.*

When you fit your patient with one of these RAMSES Diaphragms you are providing essential inner security. She is assured she can plan her family according to her wishes, safe in the knowledge that she is using not only the most reliable method—diaphragm and jelly, which reduces the likelihood of conception by at least 98 per cent[1]—but the most comfortable choice —RAMSES Diaphragm and Jelly.

1. Tietze, C.: Proceedings, Third International Conference Planned Parenthood, 1953.
*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-lasting barrier effectiveness.

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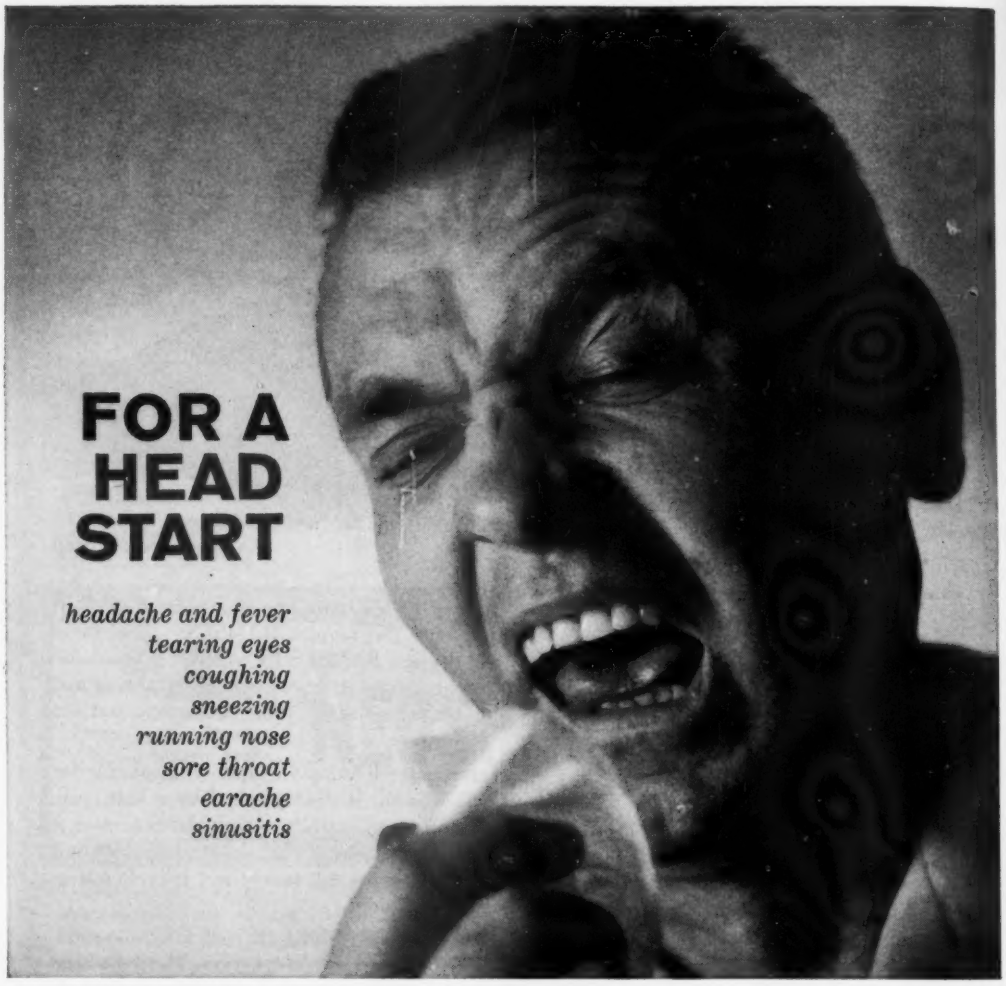

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COSA-TETRACYDIN*

glucosamine-potentiated tetracycline—analgesic—antihistamine compound

CAPSULES

- *Quick, symptomatic relief*
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Each capsule provides:

Cosa-Tetracyn	125 mg.
phenacetin	120 mg.
caffeine	30 mg.
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Additional information on Cosa-Tetracydin is available from the Medical Department of Pfizer Laboratories on request.

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an ethical answer to a medical problem

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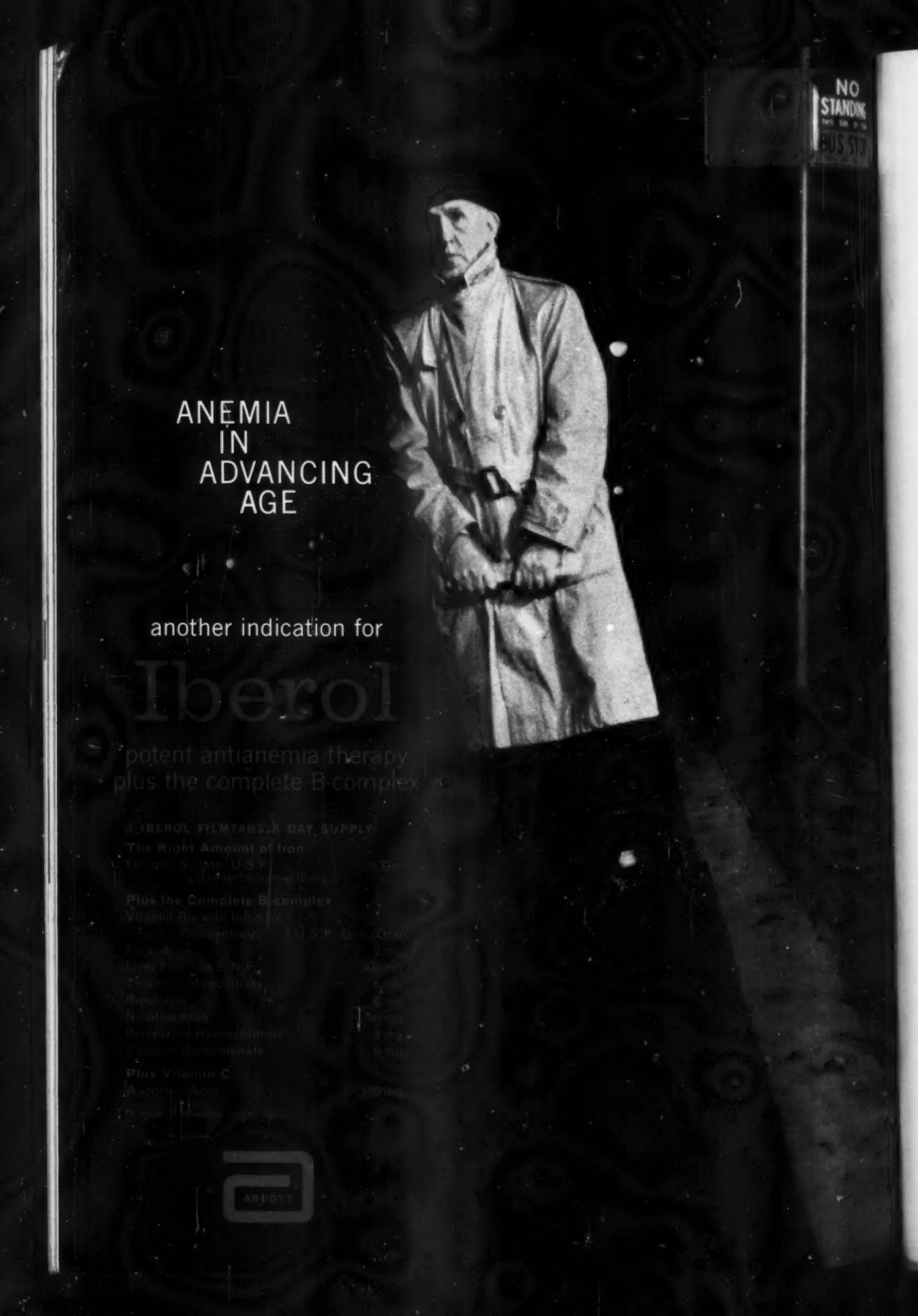
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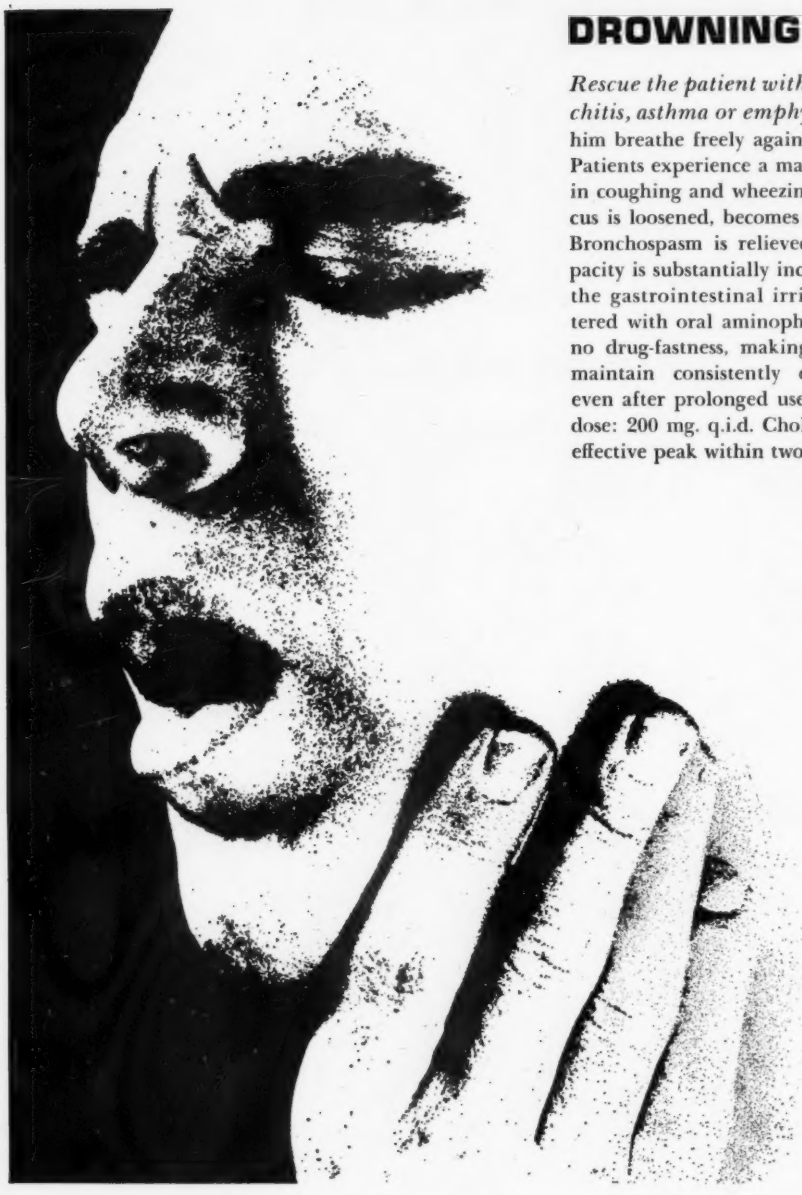

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Rescue the patient with chronic bronchitis, asthma or emphysema and help him breathe freely again with Choledyl. Patients experience a marked abatement in coughing and wheezing . . . thick mucus is loosened, becomes easier to expel. Bronchospasm is relieved, and vital capacity is substantially increased—without the gastrointestinal irritation encountered with oral aminophylline. There is no drug-fastness, making it possible to maintain consistently effective results even after prolonged use. Average adult dose: 200 mg. q.i.d. Choledyl reaches an effective peak within two weeks.

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betters breathing . . . forestalls the crisis

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in G.I. disorders

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hydroxyzine pamoate

takes him off the tension treadmill

By restoring tranquility, VISTARIL rapidly helps to relieve functional pain and discomfort in many gastrointestinal disorders. Clinicians find that patients on VISTARIL more willingly accept their condition and adhere better to their regimen.

VISTARIL has an outstanding record of safety and is valuable adjunctive therapy in home or hospital when administered to patients with peptic ulcer, gastroenteritis, esophageal spasm, and nervous dyspepsia.

A Professional Information Booklet is available from the Medical Department on request.

Supply: Capsules—25, 50 and 100 mg.; Parenteral Solution—10 cc. vials and 2 cc. Steraject® Cartridges, each cc. containing 25 mg. hydroxyzine HCl.

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in acute superficial thrombophlebitis

"A one-week course of therapy is generally sufficient to produce satisfactory resolution of the inflammatory process without recurrence."

Orbach, E. J.: J. Internat. Coll. Surgeons 31:165, 1959.

in arthritis and allied disorders

"Patients who experienced major improvement had prompt and almost complete relief of pain and stiffness, which could be maintained on a small maintenance dose."

Graham, W.: Canad. M.A.J. 79:634, (Oct. 15) 1958.

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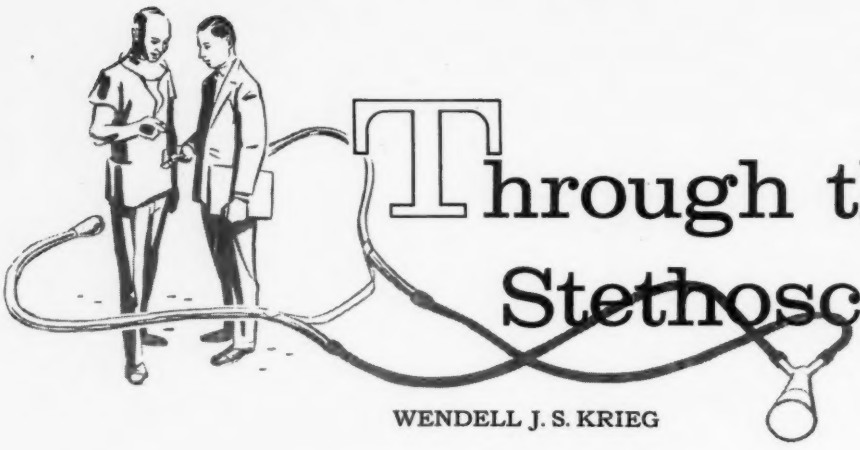


Through the Stethoscope

WENDELL J. S. KRIEG

Letters to a Medical Student

My dear son:

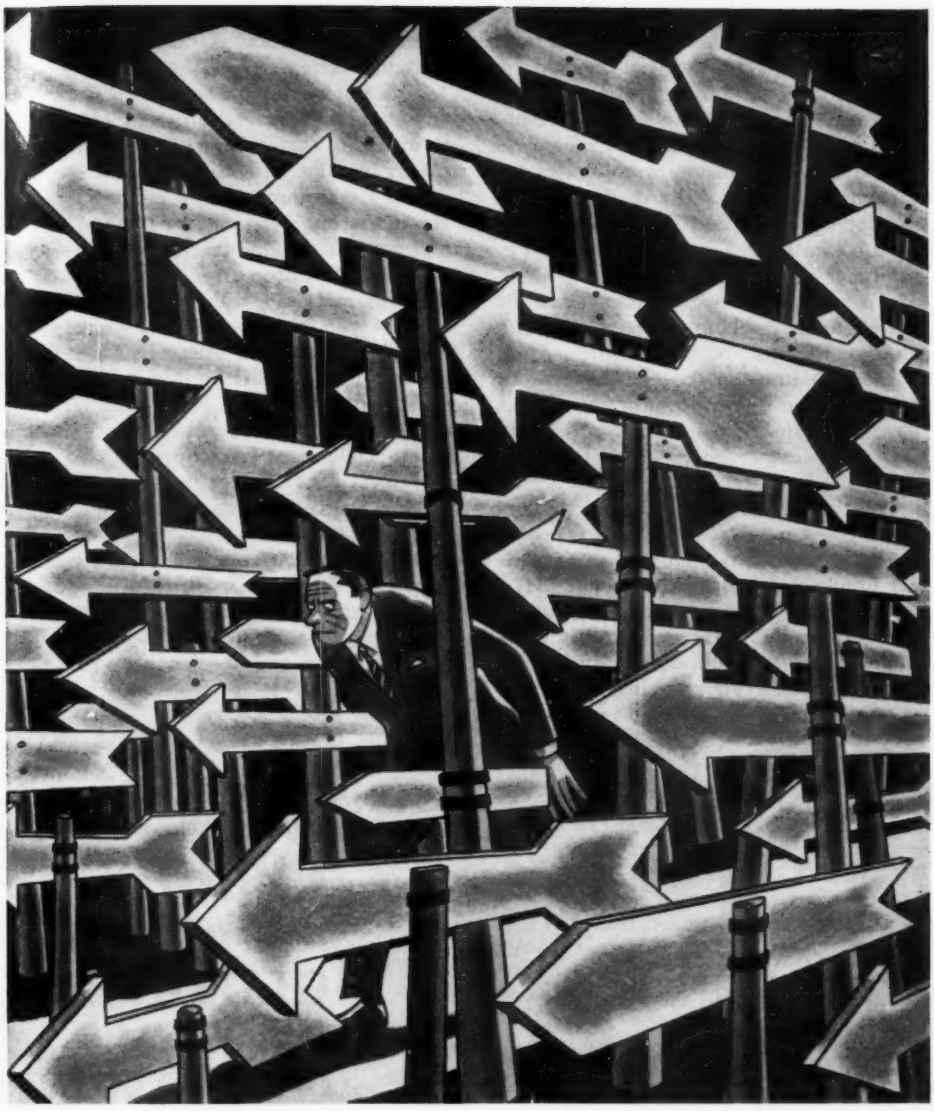
In my last letter I characterized and commented on your colleagues. However, in your earlier years, your concern in interpersonal relations will be more with your superiors than with your equals. Your reputation is based on merit, but your advancement depends partly on the personal traits of yourself and your chief, and their interaction. It would be best if we could choose a boss who is congenial to our temperament and who appreciates our qualities. This is rarely done, but if a boss chooses you, it can amount to the same thing. Bad luck it is when the man who selected you goes away and leaves you as a legacy, for the new chief may not care for your type, and your best efforts are in vain. I can say that nothing is to be gained in the home ground by redoubling them; it only increases the aggravation by making you more of a threat as you mature.

Apart from constantly working, there are two ways to conduct yourself. One is to be a "good boy" so long, so continuously and so unswervingly that finally even your superiors begin to notice it, and believing that they can depend on you (which means that you won't show them up by introducing any embarrassing innovations), they will elevate you to the next grade in rank. After such an appointment, it would be a breach of faith really to do something of your own, such as writing a textbook. In choosing such a course, you would always be afraid of what "old Jones" would think, which consideration would continually prevent you from achieving anything new, at least until old Jones retired, and then it would be too late.

The other course is to say what you really think and to do what you really believe is truest and best, trusting that "truth is mighty and will prevail," although this may belong in the same bin as "the Lord looketh after His own."

Of course, in choosing your action with relation to your superiors and administration, you should steer a course between mousiness and brashness. One can cool one's heels for a long time in anterooms, waiting for an audience, if one embraces inoffensiveness as a primary virtue. One must "step up and pat the pony." There is a moment's hesitancy, even fear, before even the most mature men make a move in a new direction; but wisdom lies in recognizing this, and the art lies in blending it in so that it is not noticed, even by yourself. I don't mean that you should jump in precipitantly, without knowledge of or regard for consequences. Try to predict objections and to have an answer ready.

(Continued on page A-96)



The constraint of rigid management

Many diabetics on insulin live highly restricted lives. They may not miss or delay a meal; they must neither over-work nor under-exercise for fear of complications.

For 3 out of 4 of these patients, Orinase* offers better control and an easier, more normal life. Because Orinase controls diabetes effectively and *smoothly* in responsive patients, they can enjoy a new freedom. And some diabetics, who cannot be managed on Orinase alone, do best on *combined* Orinase-insulin therapy.

*TRADEMARK, REG. U. S. PAT. OFF. — TOLBUTAMIDE, UPJOHN

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Upjohn **ORINASE**

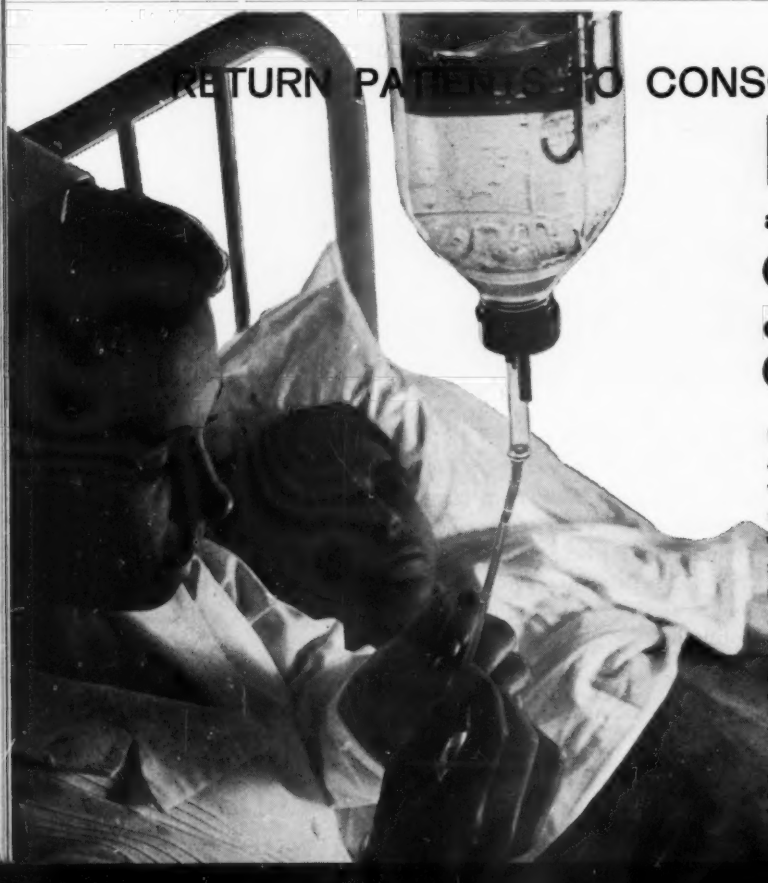
No one, whether a superior or an equal, likes a "pushy" young man. Most men in their work relationships maintain a certain restraint and modesty, and they expect others to do the same; then they are on equal terms. However, when one person clamors incessantly for privileges or facilities, or cultivates the boss's company, or seeks the dean's ear, his friends properly are resentful because he has broken the established equilibrium that fosters equity.

There is too much thought among scientific workers about the indefinite "they." If I do a good job on this, maybe "they" will see my worth. Do you imagine there is a corps of Olympians in your field who sit at great desks and have the latest publications carried to them by seraphim, to be perused in detail? This is a manifestation of the persistence of the filial attitude, the same trait in all men that leads them to create for their peace of mind a god who looks benignly down, records all, and finally reaches down his hand. No, "they" don't know about you, and "they" don't care. They are too preoccupied with committee work, advisory councils, consultations, guest appearances, staff appointments and public relations to be aware or care. Your scientific reputation is best built with your contemporaries.

I do not mean to say that one never gets anywhere by respectability and adequate performance of duties. I have seen too many pass me by for that. An old family name, a church school background, and diplomatic behavior are too strong for many executives to resist, and you can't blame them. They know that a Lowell, a Winthrop or a De Peyster won't sell them short. I only say that such an approach, even if you could evoke it, won't get you where you want to go. Rarely, indeed, is any good original work done in a high post if it is an administrative one. In science, letters and art, one attains the kingdom of heaven, like its cosmologic counterpart, by remaining humble and never ceasing to perform good works.

As long as you are nothing, you have a chance of being something; but when you receive your definitive appointment, your level is pegged, for good or ill. In arts and letters one is struck by the number of the best men who live on Vermont farms and in small Connecticut towns, and in science, by those work-

(Continued on page A-98)



RETURN PATIENTS TO CONSCIOUSNESS FROM...

hepatic coma

associated with high blood ammonia levels

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GLUTAVENE-K®

For the treatment of coma and other encephalopathies in certain liver diseases associated with high blood ammonia levels, Glutavene supplies monosodium l-glutamate and Glutavene-K supplies monosodium and monopotassium l-glutamate. These agents reduce ammonia blood levels through amidation, a reaction between glutamate and ammonia to form glutamine, a nontoxic substance.[1,2]

[illegible] For the average adult, 100 pounds or over, the contents of a 100 cc. (25 gram) vial are mixed with 1000 cc. of 5 or 10% glucose in water. This amount is given intravenously during a 4-hour period.

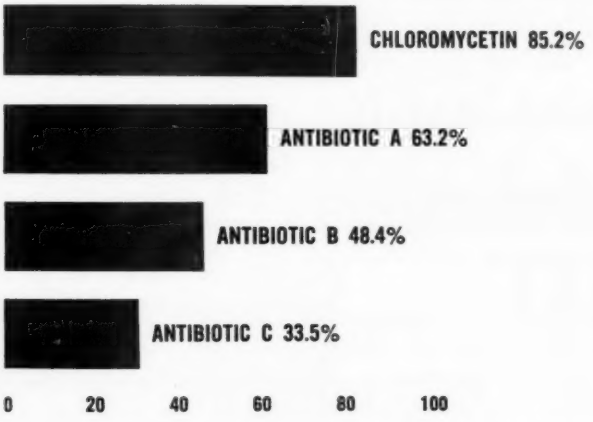
References: 1. McDermott, W. V., Jr., [illegible], J., and Riddell, A. G.: New England J. Med. 253:1093 (Dec. 22) 1955. 2. Watson, C. et al.: A.M.A. [illegible]:304 (Feb. 15) 1958.

CROOKES-BARNES LABORATORIES, [illegible]

WHEN EVEN STUBBORN HOSPITAL STAPHYLOCOCCI RESPOND... THE ANTIBIOTIC IS APT TO BE

CHLOROMYCETIN®

IN VITRO SENSITIVITY OF 337 STRAINS OF PATHOGENIC STAPHYLOCOCCI (ISOLATED FROM HOSPITAL PATIENTS) TO CHLOROMYCETIN AND TO THREE OTHER ANTIBIOTICS*



*Adapted from Goslings, W. R. O., & Büchli, K.: *Arch. Int. Med.* 102:691, 1958.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in a variety of forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its use, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

MEDICAMENTA VERA

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85259

ing in dark laboratories to whom the elevator man can't direct one, but someone in Australia can. Sometimes these men, being despaired of as potential administrators or front men, are left alone and so are able to develop. Don't be perpetually stamping in your stall or straining at the bit which curbs you from intramural recognition. In fact, local and international reputations are largely inverse, except that if an individual attains to a wide recognition away from home, an echo will surge back, with the result that he is treated with an uncomprehending awe which is sometimes mistaken for willful ignoring.

Try to keep your relation to your public in your vest pocket. If you feel you are losing your public, good deeds will regain them. People's affection and friendship are exactly in proportion to what you contribute to them, and nothing else. This contribution may be help in need, or it may be ego satisfaction. Some of the most stupid persons have the most friends, that is, if they are plastic and harmless. With women, don't be too capable or too self-sufficient. They admire blind energy, but an integrated being, a Mr. Belvedere, dismays them and turns their edge. Never try to impress or surpass your friends. You will lose them as friends, and they have been too close to become admirers. Everything in social relations ultimately comes back to the "me" side. If you make people insecure or uneasy, they will shy from you. Brilliant young men have few friends.

I believe that just as a man with greater physical power can always prevail over an opponent who is weaker, and not just in a frequency proportional to their relative strengths, so one man has greater intellectual power than another and can always prevail. I have seen the same men outsmart and outthink me too often to believe otherwise. Of course, I end by being preoccupied with them and thinking of ways to surpass them, but it never comes off. The wisdom lies in conquering what one can conquer and avoiding what one cannot.

I guess I have been a bit cynical in this letter, but I happen to be a bit stirred up today. There is time for only one more letter before you return; I promise that I will be more accepting in it.

And so, good night,
Father

NEW rapid screening test for

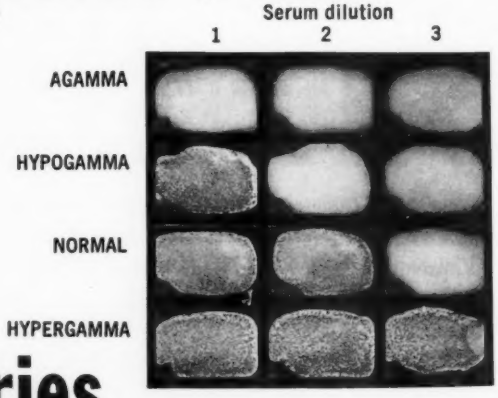
AGAMMA globulinemia

and other abnormal levels of serum gamma globulin

Hyland GG-TEST*

*Trade Mark of Hyland Laboratories

Hyland GG-TEST requires only one drop of patient's serum and is performed simply and quickly on a glass slide (reactions in less than 2 minutes). Test permits routine GG serum level determinations at low cost without overtaxing laboratory facilities. Test materials supplied in compact 40-test kits.



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meperidine-promethazine combined

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Promethazine Hydrochloride and Meperidine Hydrochloride, Wyeth

MEPERGAN provides the analgesia of meperidine augmented by the values of promethazine. These include the allaying of apprehension, the control of nausea and vomiting, the potentiation of barbiturates and narcotics, and the facilitation of anesthesia. MEPERGAN is useful in all forms of surgery. It may be used preoperatively for preparatory medication, during surgery as an adjunct to anesthesia, and postoperatively to control pain. Widespread clinical experience points to MEPERGAN's 1:1 ratio of promethazine and meperidine to be most satisfactory for most patients.

See package circular for complete information on use of MEPERGAN.

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Philadelphia 1, Pa.

*Trademark

Blood pressure
before Apresoline-Esidrix:

206/118

mm. Hg*

Blood pressure after Apresoline-Esidrix:

182/98 mm. Hg*

Added benefits: Lowered dosage requirements, fewer side effects • Improved renal blood flow • Relaxed cerebral vascular tone • Excellent diuresis in decompensated cases

SUPPLIED: Apresoline-Esidrix Tablets (orange), each containing 25 mg. of Apresoline hydrochloride and 15 mg. of Esidrix; bottles of 100.

* Response of 56-year-old female patient noted in clinical report to CIBA.

APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA) / ESIDRIX® (hydrochlorothiazide CIBA)

Apresoline®-Esidrix®

Combination Tablets

POTENTIATED ANTIHYPERTENSIVE FOR ADVANCING HYPERTENSION

SUMMIT, NEW JERSEY

Z/2746 MK

Bright
new
star
in the
antibacterial
firmament

the first nitrofuran effective orally in systemic bacterial infections

ALTAFUR™

brand of furaltadone

Effective clinically in upper respiratory infections, pneumonias, soft tissue infections, bacteremia/septicemia, osteomyelitis, wound infections and pyodermas.

Effective in vitro against the following organisms (isolated from clinical infections listed above):

Organism	*Sensitive*	*Resistant*	*% Sensitive*
Staphylococci*	181	1	*99.4*
Streptococci	65	1	*98.5*
D. pneumoniae	14	0	*100.0*
Coliforms	34	3	*91.8*
Proteus	5	5	*50.0*
A. aerogenes	8	0	*100.0*
Ps. aeruginosa	5	4	*55.5*

*Includes many strains resistant to antibiotics.

As with all nitrofurans in *years* of extensive clinical use, there is little or no development of bacterial resistance with ALTAFUR.

NITROFURANS—a unique class of antimicrobials—
neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

remember this patient with musculoskeletal pain?

remember PAIN Zactirin®

Ethoheptazine Citrate (75 mg.) with Acetylsalicylic Acid (325 mg.), Wyeth

Active now, pain relieved, inflammation controlled, *free of disturbing reactions. . . .* ZACTIRIN offers reliable analgesia plus anti-inflammatory benefits in a wide variety of joint and muscle disorders. It is non-narcotic and nonsteroid. Its relief of pain is equivalent to that of codeine. Yet it is well tolerated in both acute and prolonged use.

Myositis, fibrositis, myalgia, low back pain, ligamental strain, sciatica, bursitis, frozen shoulder, wryneck, osteoarthritis, rheumatoid arthritis, postoperative orthopedics

Supplied: Tablets, bottles of 48.

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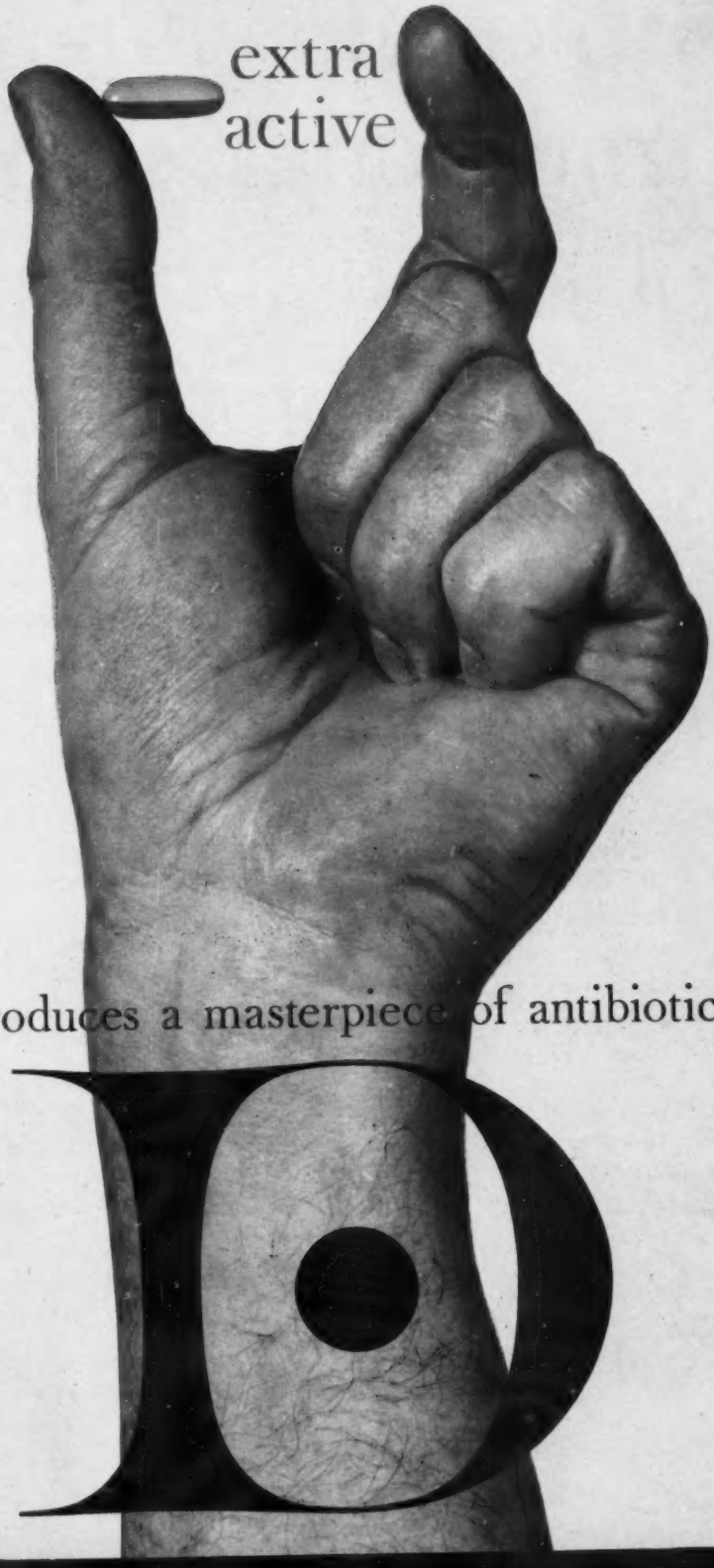


Lederle introduces a masterpiece of antibiotic design

Strikingly enhances the traditional advantages of broad-spectrum antibiotics...

for greater patient-physician benefit

DECLOMYCIN is a unique fermentation product of a strain of *Streptomyces aureofaciens*—the parent organism of AUREOMYCIN®* and ACHROMYCIN.®†

DECLOMYCIN singularly achieves:

- far greater antibiotic activity with far less drug
- greater stability in body media
- unrelenting peak activity throughout therapy
- "extra-day" protection through sustained activity

DECLOMYCIN retains:

- unsurpassed broad-spectrum range of activity
- rapid activity
- excellent toleration
- effectiveness against infection in nearly all organs or systems—rapid diffusion in body tissues and fluids

**Chlortetracycline Lederle* †*Tetracycline Lederle*

DECLO

Demethylchlortetracycline Lederle

Far greater antibiotic activity with far less antibiotic

Milligram for Milligram, DECLOMYCIN exhibits 2 to 4 times the clinical potency (inhibitory action) of tetracycline against susceptible organisms. Thus, DECLOMYCIN has the advantage of providing significantly higher serum *activity* levels with significantly reduced drug intake.* [1,3,5]

Actually, DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of milligram intake of drug reduces hazards of related physical effect on intestinal mucosa or interaction with gastrointestinal contents.

*Activity level is a far more meaningful basis of comparison than quantitative blood levels, as Hirsch and Finland note. Action upon pathogens is the ultimate value.[1]

OMYCIN

Unrelenting peak antimicrobial attac throughout therapy

The high level of DECLOMYCIN activity is uniquely sustained. It is not just an initial phenomenon but is constant—maintained on each day of treatment and between doses—without noticeable diminution of intensity. Peak-and-valley control is eliminated, favoring continuous suppression of pathogens and consequent improvement.

This DECLOMYCIN constant is achieved through remarkably greater stability in body fluids,[2,4,6] resistance to degradation[6] and a low rate of renal clearance[4,5]—all supporting antibiotic activity for extended periods.

DECLO

Demethylchlortetracycline Lederle

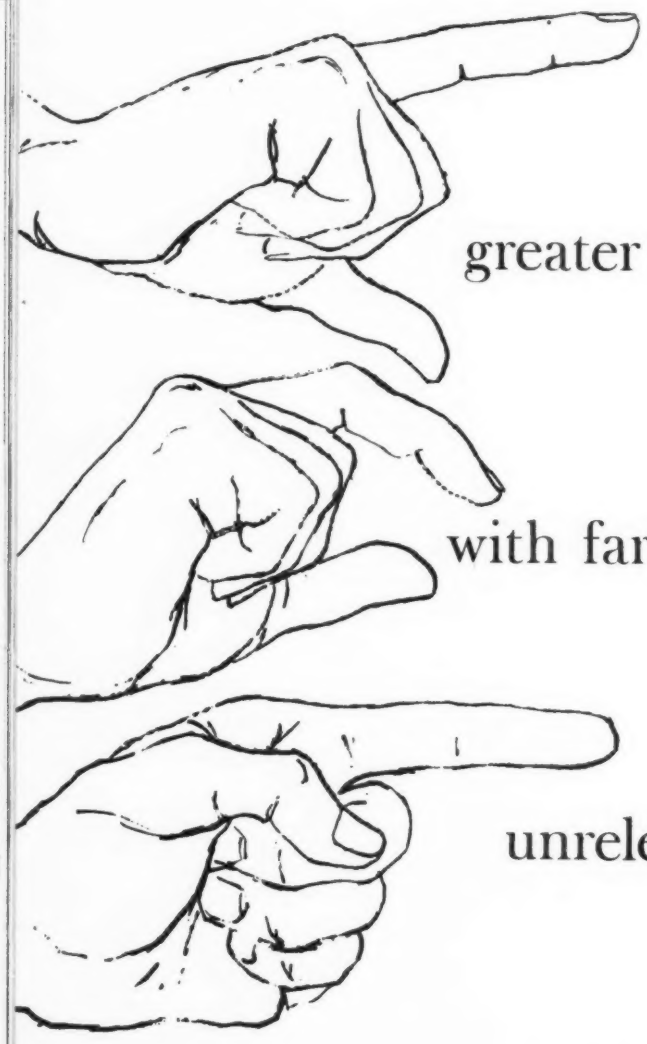
"Extra-day" activity for security against relapse

DECLOMYCIN maintains significant antibacterial activity for one to two days after discontinuance of dosage[1]—a major distinction from other antibiotics. Previous drugs have declined abruptly in activity following withdrawal.

DECLOMYCIN thus gives the patient an unusual degree of protection against resurgence of the primary infection, and against secondary infection... sequelae not infrequently encountered and often resembling a "resistance problem." Consequently, reinstitution of therapy or a change in therapy should rarely be necessary.

MYCIN

A masterpiece of an



greater antibiotic activity

with far less antibiotic intake

unrelenting peak attack

—enhancing the unsurpassed features of tetracycline . . . for greater physician-patient benefits

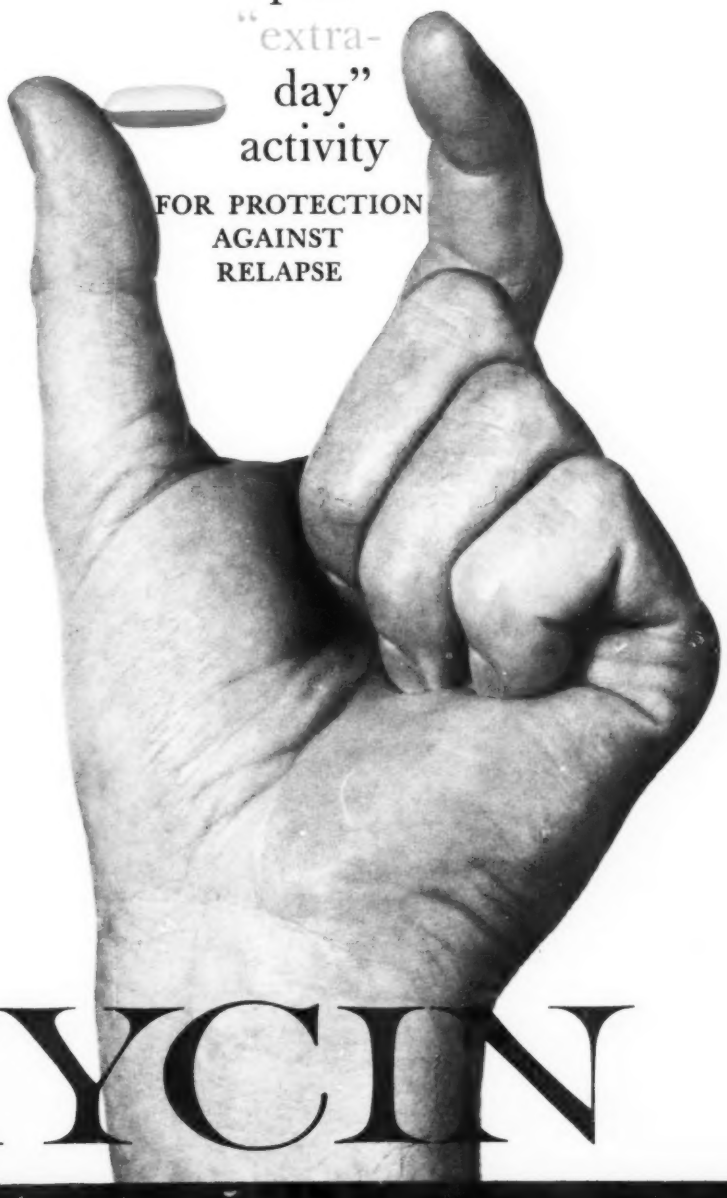
DECLO

Demethylchlortetracycline Lederle

antibiotic design

plus
"extra-
day"
activity

FOR PROTECTION
AGAINST
RELAPSE



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in the distinctive dry-filled duotone capsule

DECLOMYCIN

Demethylchlortetracycline Lederle

available as:

DECLOMYCIN Capsules, 150 mg.
Adult dosage: 1 capsule four times daily.
Pediatric Drops, 60 mg. per cc.
Bottles of 10 cc. with dropper.
Oral Suspension, 75 mg. per 5 cc. tsp.

1. Hirsch, H. A., and Finland, M.: Antibacterial Activity Of Serum Of Normal Subjects After Oral Doses of Demethylchlortetracycline, Chlortetracycline and Oxytetracycline. *New England J. Med.* 260:1099 (May 28) 1959. 2. Hirsch, H. A., Kunin, C. M., and Finland, M.: Demethylchlortetracycline – A New And More Stable Tetracycline Antibiotic That Yields Greater and More Sustained Antibacterial Activity. To be published. 3. Lichter, E. A., and Sobel, S.: The Distribution Of Oral Demethylchlortetracycline In Healthy Volunteers And In Patients Under Treatment For Various Infections. To be published. 4. Kunin, C. M., Dornbush, A. C. and Finland, M.: Distribution And Excretion Of Four Tetracycline Analogues In Normal Young Men. To be published. 5. Kunin, C. M., and Finland, M.: Demethylchlortetracycline: New Tetracycline Antibiotic That Yields Greater and More Sustained Antibacterial Capacity. *New England J. Med.* 259:999 (Nov. 20) 1958. 6. Sweeney, W. M.; Hardy, S. M.; Dornbush, A. C., and Ruegsegger, J. M.: Demethylchlortetracycline: A Clinical Comparison of A New Antibiotic with Chlortetracycline and Tetracycline. *Antibiotics & Chemotherapy* 9:13 (Jan.) 1959.

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Declomycin Caps
150 mg.
Disp # XVI
Sig 1 cap q.i.d.

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a Division of AMERICAN CYANAMID COMPANY
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Lederle

Traffic: jammed
Car: stalled

Temper: mild
Ulcer: quiet

Here's a man whose ulcer once would have protested strongly—not just at traffic problems—but at the entire gamut of stress to which modern man is subjected.
His physician, aware that *the patient as well as the ulcer* must be treated, has prescribed ALUDROX SA.

eases tension • promotes healing
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Suspension and Tablets: Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide and Butabarbital, Wyeth

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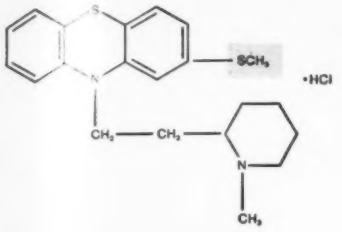
ANNOUNCING SCHERING'S NEW MYOGESIC[X]

RELA™ EASES STRAINS SPRAINS & LOW BACK PAINS...!

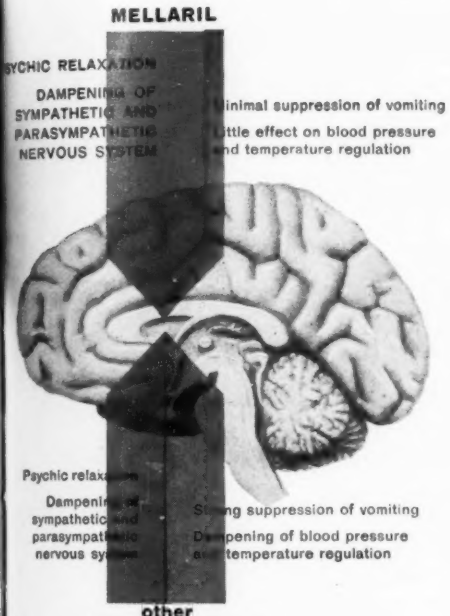
CARISOPRODOL

new advance in tranquilization:
greater specificity of tranquilizing action results in fewer side effects



The presence of a thiomethyl radical (S-CH₃) is unique in Mellaril and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

1 **A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.**


MELLARIL
PSYCHIC RELAXATION
DAMPENING OF SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEM
Minimal suppression of vomiting
Little effect on blood pressure and temperature regulation
Psychic relaxation
Dampening of sympathetic and parasympathetic nervous system
Suppression of vomiting
Dampening of blood pressure and temperature regulation
other phenothiazine-type tranquilizers

2 **Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.**

3 **A notable absence of extrapyramidal stimulation.**

4 **Lack of impairment of patient's normal drive and energy.**

5 **Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.**

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
ADULTS: Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
CHILDREN: BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

LLARIL Tablets, 10 mg., 25 mg., 100 mg.

ld, A. M.: Scientific Exhibit, American Academy General Practice, San Francisco, April 6-9, 1959.

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INTRAMUSCULAR IRON-DEXTRAN COMPLEX

corrects and prevents iron deficiency in blood and marrow

PEDIATRICS: "IMFERON has the advantage of safe and easy administration; treatment is completed in a few days and is not influenced by feeding problems."[1]

OBSTETRICS: "...we have been able to raise hemoglobin levels of 7 or 8 Gm. to normal figures within a few weeks...."[2]

CHRONIC BLOOD LOSS: IMFERON "...is also to be preferred to blood transfusions for correcting the effects of chronic blood loss. The risk of transfusion reactions is avoided, as well as the dangers of contamination and sensitization. Besides improving the anemia, iron stores will be replenished...."[3]

GERIATRICS: A 66-year-old woman with recurrent gastrointestinal bleeding for over six years [two abdominal explorations, source undiscovered] "...has been maintained at a comfortable blood level for over nine months on intramuscular iron injection, with greatly reduced transfusion requirement."[4]

SUPPLIED: 2-cc. and 5-cc. ampuls; 10-cc. multiple-dose vials. There are 50 mg. of elemental iron per cc.

(1) Wallerstein, R. O., and Hoag, M. S.: J.A.M.A. **164**:962 (June 29) 1957. (2) Eastman, N. J.: Current M. Dig. **25**:55 (Jan.) 1958. (3) Koszewski, B. J., and Walsh, J. R.: Am. J. M. Sc. **235**:523 (May) 1958. (4) McCurdy, P. R.; Rath, C. E., and Meerkrebs, G. E.: New England J. Med. **257**:1147 (Dec. 12) 1957.

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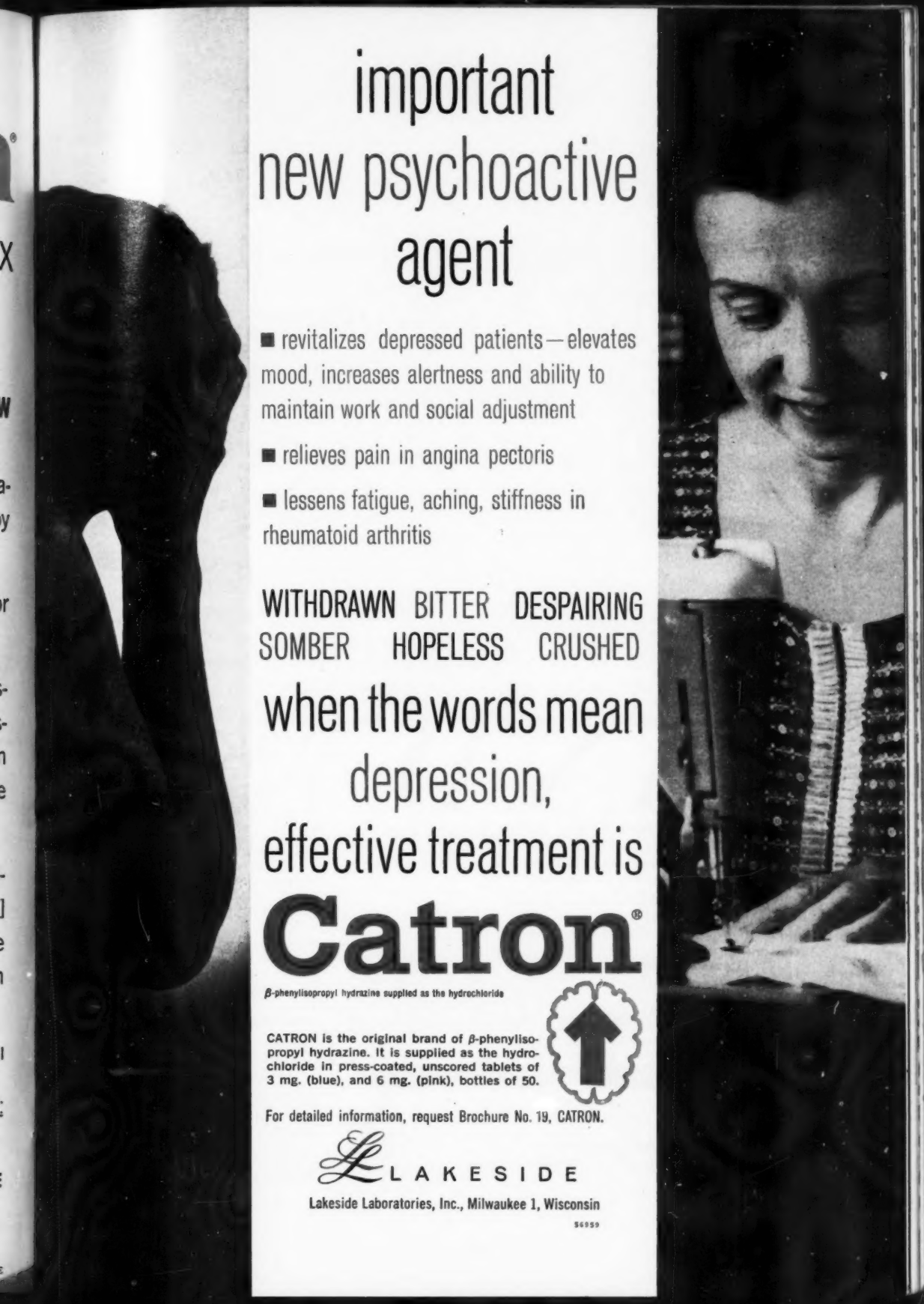
LAKESIDE



important new psychoactive agent

- revitalizes depressed patients—elevates mood, increases alertness and ability to maintain work and social adjustment
- relieves pain in angina pectoris
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WITHDRAWN BITTER DESPAIRING
SOMBER HOPELESS CRUSHED

when the words mean depression, effective treatment is

Catron®

β-phenylisopropyl hydrazine supplied as the hydrochloride

CATRON is the original brand of β-phenylisopropyl hydrazine. It is supplied as the hydrochloride in press-coated, unscored tablets of 3 mg. (blue), and 6 mg. (pink), bottles of 50.

For detailed information, request Brochure No. 19, CATRON.

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56959

New Enzyme-controlled antifungal therapy to meet the growing challenge of **Monilial Vaginitis**

IN PREGNANCY / IN DIABETES / AFTER ANTIBIOTIC THERAPY–Today, monilial vaginitis is estimated to be a problem in at least 33 per cent of pregnant women and about 10 per cent of nonpregnant females[1]—a rapidly increasing incidence attributed partly to the widespread use of antibiotics.

"Vanay" Vaginal Cream broadens the scope of specific therapy: (1) "Vanay" insures a continuous therapeutic fungistatic effect without danger of local reaction; (2) in addition, "Vanay" restores and maintains a physiologic pH and normal vaginal flora—reducing risk of reinfection.

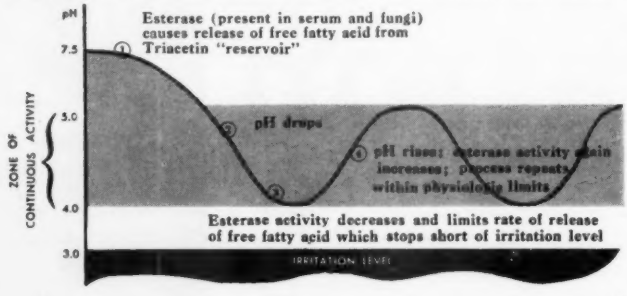
Effective response: Treatment was notably effective in moniliasis, as confirmed by symptomatic relief and post-treatment smears, Assali reports.[2] Marked clinical improvement was also noted in 154 of 206 patients, and in some cases symptoms subsided within a week of therapy.[3]

Other advantages: No monilial resistance demonstrated[4] / prolonged duration of activity[4] / nonsensitizing / nonirritating / nonstaining / odorless.

"VANAY" Vaginal Cream

BRAND OF TRIACETIN IN NONLIQUEFYING BASE

UNIQUE ENZYME-CONTROLLED FUNGISTASIS WITHOUT IRRITATION[3,4]


pH
7.5
5.0
4.0
3.0
ZONE OF CONTINUOUS ACTIVITY
Esterase (present in serum and fungi) causes release of free fatty acid from Triacetin "reservoir"
pH drops
pH rises; esterase activity again increases; process repeats within physiologic limits
Esterase activity decreases and limits rate of release of free fatty acid which stops short of irritation level
IRRITATION LEVEL

Indications: specific in monilial vaginitis...adjunctive in trichomoniasis . . . also valuable in nonspecific vaginitis where an acid pH must be restored and maintained.

Usual Dosage: 2 to 4 grams daily.

Supplied: No. 204-250 mg. Glyceryl triacetate per gram in a nonliquefying base. Combination package: 1½ oz. tube with 15 disposable applicators.

References: 1. Idson, B.: Drug & Cosmetic Industry *84*:30 (Jan.) 1959. 2. Assali, N. S.: Personal communication. 3. Combined results of 18 clinical investigators, Medical Records, Ayerst Laboratories. 4. Kubista, R. A., and Derse, P. H.: Antibiotics & Chemotherapy, to be published. 5. Knight, S. G.: J. Invest. Dermat. *28*:363 (May) 1957. 6. Knight, S. G.: Antibiotics & Chemotherapy 7:172 (Apr.) 1957.

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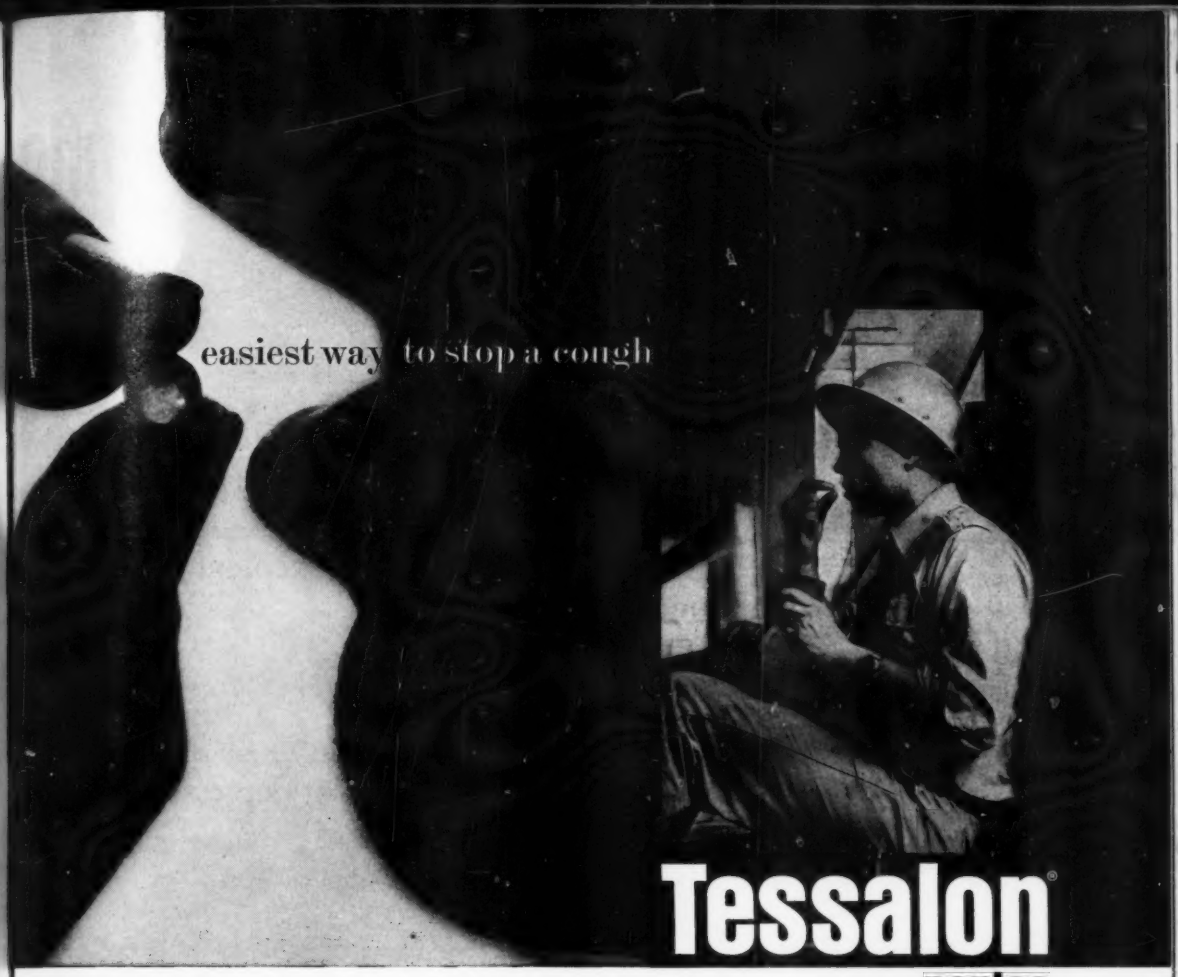
Patent Applications Pending



Tessalon®

perles

Tessalon perles stop cough fast—and they're convenient to take. No mess, no spillage, no awkward spoons or bottles to carry around. Another advantage: *no taste*. An exact, effective dose is sealed in a tiny gelatin sphere.

Reasons *why* Tessalon stops cough so effectively: it acts where cough begins—in the chest; it acts at the cough reflex center—in the medulla; it acts promptly—within 15 to 20 minutes, the effect lasting up to 8 hours. Tessalon is *not* a narcotic, yet has been reported 2½ times more effective than codeine in suppressing cough.[1]

SUPPLIED: Tessalon *Perles*, 100 mg. (yellow); bottles of 100. Tessalon *Pediatric Perles* (for children under 10), 50 mg. (red); bottles of 100. *Also available* (for use when oral administration of Tessalon is precluded): *Ampuls*, 1 ml. (5 mg.); cartons of 5.

1. Shane, S. J., Krzyaki, T. K., and Copp, S. E.: Canad. M. A. J. 77:600 (Sept. 15) 1957.

Remember
SERPASIL®
(reserpine CIBA)
for the anxious hypertensive with or without tachycardia

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TESSALON® (benzonatate CIBA)

CIBA
Summit, New Jersey

Tofrānil® a thymoleptic

brand of imipramine HCl

Specific in Depression

does

Produce remission or improvement in 70-85% of cases

Act effectively in all types of depression

Afford equally good results in severe as in mild cases

Achieve therapeutic benefit with minimal risk of serious side reaction

Indications for Tofrānil include:

Endogenous Depression, Reactive Depression, Involutional Melancholia, Senile Depression, Depression associated with other Psychiatric Disorders.

Availability: Tofrānil (brand of imipramine HCl) tablets of 25 mg. bottles of 100. Ampuls of 25 mg. (for intramuscular administration only) cartons of 10 and 50.

.....not a MAO inhibitor

does not

Inhibit monoamine oxidase either in brain or liver with its associated risks

Produce dangerous potentiation of other drugs such as barbiturates and alcohol

Act by producing undesirable central nervous stimulation leading to agitation and excitement

Cause disturbance of color vision

The efficacy of Tofranil is attested by more than 50 published reports and confirmed by clinical experience in more than 50,000 cases.

Detailed Literature Available on Request.

Geigy, Ardsley, New York

Geigy

the anatomy of touch... EXQUISITE SENSIBILITY

An alert and exquisite "fifth sense" in clinical diagnosis is tactile sensibility, as, for example, in discerning the presence and quality of a nodule in the thyroid.

Patients esteem their own tactile sensibilities, as well, and notably in the choice of a prophylactic, RAMSES,® for example, in which utmost sensitivity is preserved—"built-in." The superior prophylactic, RAMSES is a tissue-thin rubber sheath of amazing strength, of solid clinical reliability, and yet smooth as silk, transparent as gossamer, almost out of human awareness.

RAMSES enables the physician to rely on rigorous cooperation for putting an end to the cycle of re- and re-infection with Trichomonas,[1] due most often to unprotected sexual intercourse.[2] Without imposition, or deprivation, for the sake of cure, routinely using RAMSES will assure positive clinical control with a minimum of awareness, for in RAMSES the sensitivity is "built-in."

RAMSES®
PROPHYLACTICS

Pacini's corpuscle (pressure sensibility)

Meissner's corpuscle (tactile information)

Ruffini's spindle (warmth)

1. Weiner, H. H.: Clin. Med. 5:25 (Jan.) 1958.
2. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. 76:666 (Sept.) 1958.

JULIUS SCHMID, INC., 423 West 55th Street, New York 19, N. Y.

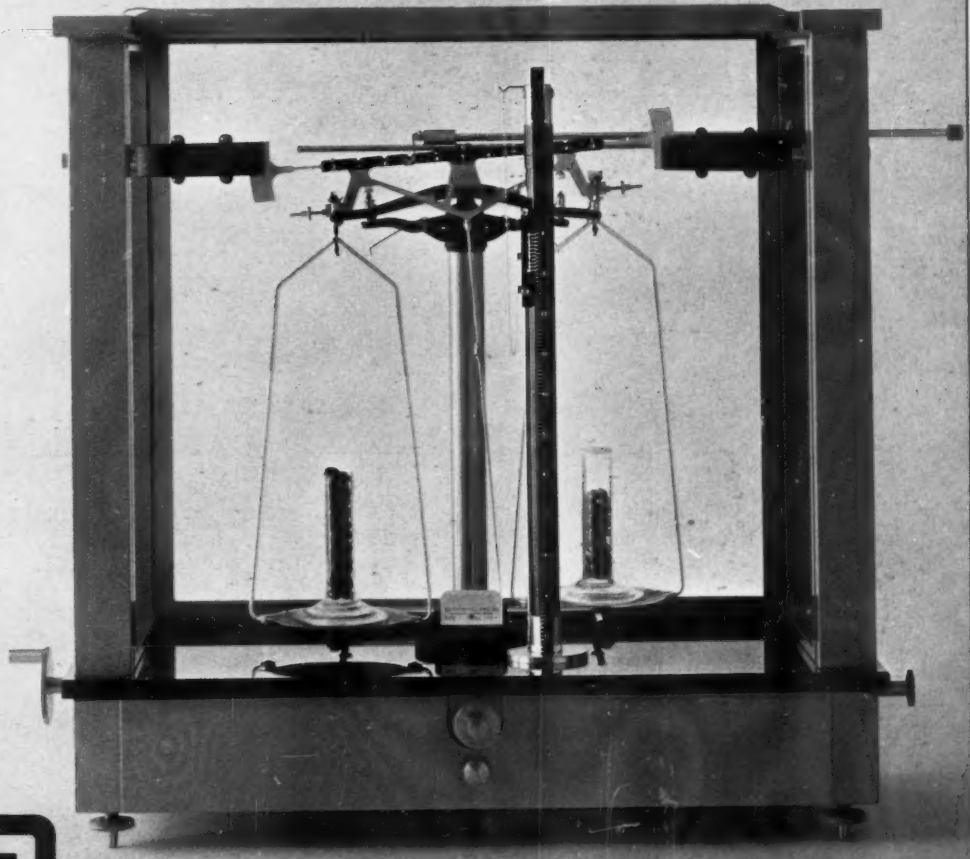
RAMSES is a registered trade-mark of Julius Schmid, Inc.

WHAT MAKES ABBOTT VITAMINS SO SMALL?

Take this Dayalets-M® for example. It contains nineteen ingredients—10 important vitamins plus nine valuable minerals. Yet it's no larger than a Spanish peanut—easily the most compact tablet of its kind. Likewise with the Abbott vitamins listed on the next page.

Secret? One word. Filmtab®. Microscopically thin, this ingenious tablet coating (an Abbott exclusive) cuts the tablet weight as much as one half, reduces bulk up to a third.* Small point perhaps—but a nice one for your patient. The coating also seals out vitamin taste and odor—and resists chipping and deterioration. All of these things make Abbott vitamins just a little easier to take—a little pleasanter to keep on the table.

**When compared to some sugar-coated tablets. Below: 25 sugar-coated Dayalets-M on left pan of scale; 25 Filmtab Dayalets-M on right. Note the difference in volume and weight.*



ABBOTT

And only Abbott offers a full line of multivitamins in "table bottles"—at no extra cost to your patient (see other side).

®FILMTAB—FILMTAB-SEALED TABLETS; ABBOTT, U.S. PAT. NO. 2,881,089 —911036A

VITAMINS BY ABBOTT

IN THE EXCLUSIVE FILMTAB COATING, WHICH CUTS THE SIZE . . .
IN THE ABBOTT "TABLE BOTTLES" WHICH HELPS THEM REMEMBER

PRODUCT AND HOW SUPPLIED	FORMULA/DOSAGE	DESCRIPTION
filmtab **DAYALETS®** Table bottle (100's); bottles of 50 & 250 filmtab **DAYALETS-M®** Apothecary bottles, 100 & 250.	each Filmtab **DAYALETS** represents: Vitamin A ..... 3 mg. (10,000 units) Vitamin D ..... 25 mcg. (1000 units) Thiamine Mononitrate ..... 5 mg. Riboflavin ..... 5 mg. Nicotinamide ..... 25 mg. Pyridoxine Hydrochloride ..... 2 mg. Vitamin B_{12} (as cobalamin concentrate) ..... 2 mcg. Folic Acid ..... 0.25 mg. Calcium Pantothenate ..... 5 mg. Ascorbic Acid ..... 100 mg. **Dosage:** Just one Filmtab daily for prophylaxis; two or more daily for therapeutic effect. each **DAYALETS-M** represents all of Dayalets' vitamins, plus the following: Iron (as sulfate) ..... 10 mg. Copper (as sulfate) ..... 1 mg. Iodine (as calcium iodate) ..... 0.15 mg. Cobalt (as sulfate) ..... 0.1 mg. Manganese (as sulfate) ..... 1 mg. Magnesium (as oxide) ..... 5 mg. Potassium (as sulfate) ..... 5 mg. Zinc (as sulfate) ..... 1.5 mg. Molybdenum (as sodium molybdate) .. 0.2 mg. **Dosage:** One Filmtab daily for prophylaxis; in more severe deficiencies, more may be prescribed.	Two extra-potent maintenance formulas; ideal for those who are "run-down" nutritionally, or as prophylaxis for those on a restricted diet.
filmtab **OPTILETS®** **OPTILETS-M®** Table bottles of 30 and 100. Bottles of 50 and 1000.	Each **OPTILETS** Filmtab represents: Vitamin A ..... 7.5 (25,000 units) Vitamin D ..... 25 mcg. (1000 units) Thiamine Hydrochloride ..... 10 mg. Riboflavin ..... 5 mg. Nicotinamide ..... 100 mg. Pyridoxine Hydrochloride ..... 5 mg. Folic Acid ..... 0.3 mg. Vitamin B_{12} (as cobalamin concentrate) ..... 6 mcg. Calcium Pantothenate ..... 20 mg. Ascorbic Acid ..... 200 mg. **Dosage:** One or two Filmtabs daily, as directed by physician. each **OPTILETS-M** represents all the vitamins of Optilets, plus the following: Iron (as sulfate) ..... 10 mg. Copper (as sulfate) ..... 1 mg. Iodone (as calcium iodate) ..... 0.15 mg. Cobalt (as sulfate) ..... 0.1 mg. Manganese (as sulfate) ..... 1 mg. Magnesium (as oxide) ..... 5 mg. Potassium (as sulfate) ..... 5 mg. Zinc (as sulfate) ..... 1.5 mg. Molybdenum (as sodium molybdate) .. 0.2 mg. **Dosage:** One or two Filmtabs daily, as directed by physician.	Therapeutic formulas for the more severe deficiencies—excellent for use when bodily stresses and requirements are increased, as in periods of illness or infection.
filmtab **SUR-BEX® with C** Table bottle of 60. Bottles of 100, 500 and 1000.	each **SUR-BEX WITH C** Filmtab represents: Thiamine Mononitrate ..... 6 mg. Riboflavin ..... 6 mg. Nicotinamide ..... 30 mg. Pyridoxine Hydrochloride ..... 1 mg. Vitamin B_{12} ..... 2 mcg. (as cobalamin concentrate) Calcium Pantothenate ..... 10 mg. Ascorbic Acid ..... 150 mg. Desiccated Liver, N.F. ..... 300 mg. Brewer's Yeast, Dried ..... 150 mg. **Dosage:** As a dietary supplement, 1 or 2 Filmtabs daily; in convalescence, 2 or more Filmtabs daily.	The complete B-complex formula with a therapeutic amount of ascorbic acid . . . especially useful during such periods as postoperative recovery when the water soluble vitamins can be rapidly depleted.

For the first time

CONVENIENCE · ECONOMY

in parenteral Broad-Spectrum antibiotic therapy

TERRAMYCIN®

brand of oxytetracycline

INTRAMUSCULAR SOLUTION

New ready-to-inject ampule form provides economical Broad-Spectrum activity for that all-important first dose.

Supplied: Terramycin Intramuscular Solution*
100 mg./2 cc. ampule
250 mg./2 cc. ampule

*Contains 2% Xylocaine® (lidocaine), trademark of Astra Pharmaceutical Products, Inc.

Complete information on Terramycin Intramuscular Solution is available through your Pfizer Representative or the Medical Department, Pfizer Laboratories.

Pfizer *Science for the world's well-being™* Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

"I've heard there's an antispasmodic with near-certain results. What's its name?"
"Bentyl. More than 85% effective, yet non-mydriatic and safe even in glaucoma."
TRADEMARK: BENTYL® (DICYCLOMINE) HYDROCHLORIDE
For fast, sure ... safe relief of G.I. spasm ... pain, prescribe Bentyl 20 mg. with Phenobarbital. Dosage: 2 capsules t.i.d.
The Wm. S. Merrell Company, New York ... Cincinnati • St. Thomas, Ontario
Merrell

COMPATIBLE · COORDINATED ANTIBIOTIC THERAPY

New TERRAMYCIN

oxytetracycline with polymyxin B sulfate

INTRAMUSCULAR SOLUTION

Initiation of therapy in *minutes after diagnosis* with new, ready-to-inject Terramycin Intramuscular Solution provides maximum, sustained absorption of potent broad-spectrum activity.

Supply:
*Terramycin Intramuscular Solution**
100 mg./2 cc. ampule
250 mg./2 cc. ampule

COSA-TERRAMYCIN

oxytetracycline with phenazopyridine

CAPSULES

Continuation with oral Cosa-Terramycin every six hours will provide highly effective antibacterial serum and tissue levels for prompt infection control.

Cosa-Terramycin Capsules
125 mg. and 250 mg.

Cosa-Terramycin is also available as:
Cosa-Terramycin Oral Suspension
peach flavored, 125 mg./5 cc., 2 oz. bottle
Cosa-Terramycin Pediatric Drops
peach flavored, 5 mg./drop (100 mg./cc.), 10 cc. bottle with calibrated dropper

The unsurpassed record of clinical effectiveness and safety established for Terramycin is your guide to successful antibiotic therapy.

Complete information on Terramycin Intramuscular Solution and Cosa-Terramycin oral forms is available through your Pfizer Representative or the Medical Department, Pfizer Laboratories.

Pfizer *Science for the world's well-being*™ PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

*Contains 2% Xylocaine® (lidocaine), trademark of Astra Pharmaceutical Products, Inc.

Before Esidrix:
Weight 176 lbs.

27 pounds lost in 19 days; ascites and

RECORD OF TREATMENT (At a leading New York City hospital. Photos used with permission of the patient.)

Date	3/3	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23
Weight (pounds)	178	176	170	169	167	159	158	158	157	153	155	155	156	154	153	154	153	—	—	151	149
Rx	M*		Esidrix 50 mg. b.i.d.																		

*Mercurial diuretic

Esidrix T.M.

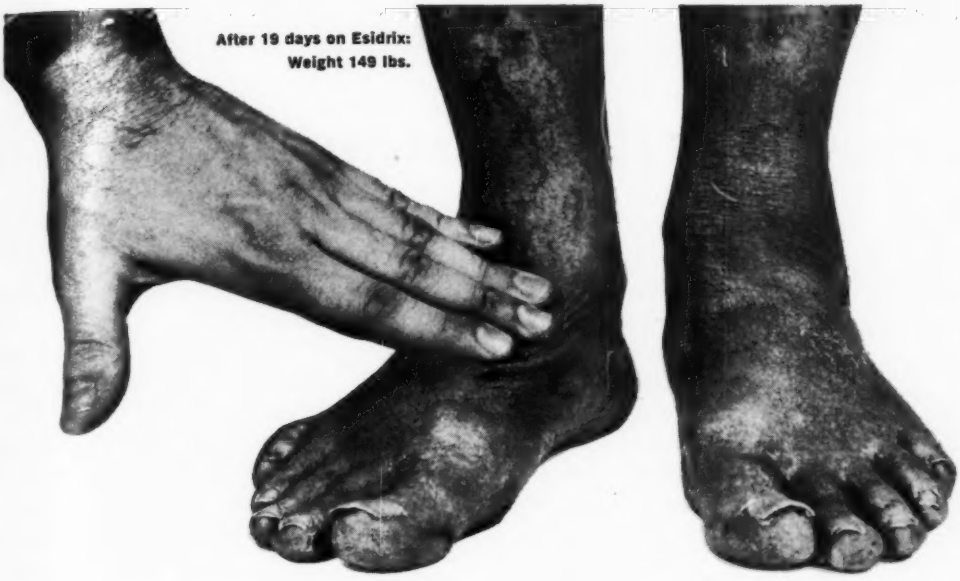
(hydrochlorothiazide CIBA)

pre-eminently effective whenever diuresis is desired

Indicated in: congestive heart failure . . . nephrosis and nephritis . . . toxemia of pregnancy . . . premenstrual edema . . . edema of pregnancy . . . steroid-induced edema . . . edema of obesity

Supplied: Esidrix *Tablets,*
25 mg. (pink, scored)
and 50 mg. (yellow, scored);
bottles of 100 and 1000.

CIBA
SUMMIT, N. J.



pedal edema reduced with Esidrix

H. K., 44 years old, was admitted to the hospital on 3/3/59 with complaints of *swollen abdomen, swelling of both legs and exertional dyspnea.* These symptoms had been intensifying over a three-week period. The patient's history included heavy drinking since the age of 18, and one prior admission to the hospital in 1954 with ascites and pedal edema. Diagnosis, at that time, was Laennec's cirrhosis, and the patient responded well to a regimen of diuretics, salt restriction and multivitamins. There was no recurrence up to that leading to his current admission.

2/2714MK

Clinical findings worthy of note: Eyes – conjunctivae and sclerae slightly icteric. Chest—diaphragm elevated. Abdomen – girth enlarged, definite fluid wave. Liver palpated 4 fingerbreadths below the costal margin; no other palpable viscera. Extremities—pedal edema (4+).

The patient is well developed and not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min. Impression: Laennec's cirrhosis—decompensated.

Treatment: Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.

announcing

the keystone in a new and eff

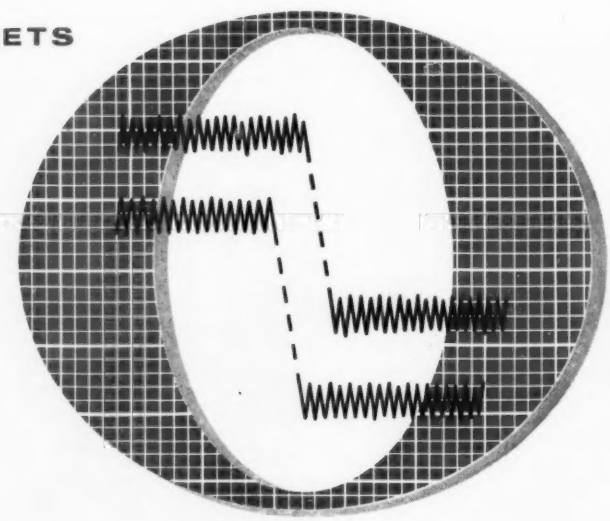
OSTENSIN is a new oral ganglionic-blocking agent of significance to ever physician who treats hypertensive patients. The sympathetic blockad produced with OSTENSIN lowers systolic and diastolic blood pressure wit predictable effectiveness and yet—because of minimal parasympathet action—with fewer and less severe by-effects.[1,2,3] OSTENSIN offers furth advantages in oral administration, low dosage, smooth and prolonge antihypertensive action, prompt onset, no evidence of inherent toxicit and rare drug tolerance.[3]

OSTENSIN, used with chlorothiazide or its derivatives, provides a superi new antihypertensive regimen[1,2,3,4] with reduced dosage, by-effects fu ther decreased, and maximal clinical benefits.

OSTENSIN is indicated in diastolic hypertension. (Diastolic hypertensio is defined as ". . . the elevation of diastolic blood pressure to 90 mm. H or above."[5])

COMPREHENSIVE LITERATURE SUPPLIED ON REQUEST

TABLETS



Wyeth®
Philadelphia 1, Pa.

OSTENSIN is the registered trademark for Trimethidinium Methosulfate, Wyeth.

...effective antihypertensive regimen

By-Effects of Three Other Ganglionic-Blocking Agents[6,7,8] Compared with Those of Ostensin[1,9]

	Other Agents	OSTENSIN
Constipation	59-69% of patients	5% of patients
Postural hypotension	33-59% of patients	37% of patients
Visual disturbances	42-50% of patients	34% of patients
Dry mouth	38-41% of patients	15% of patients

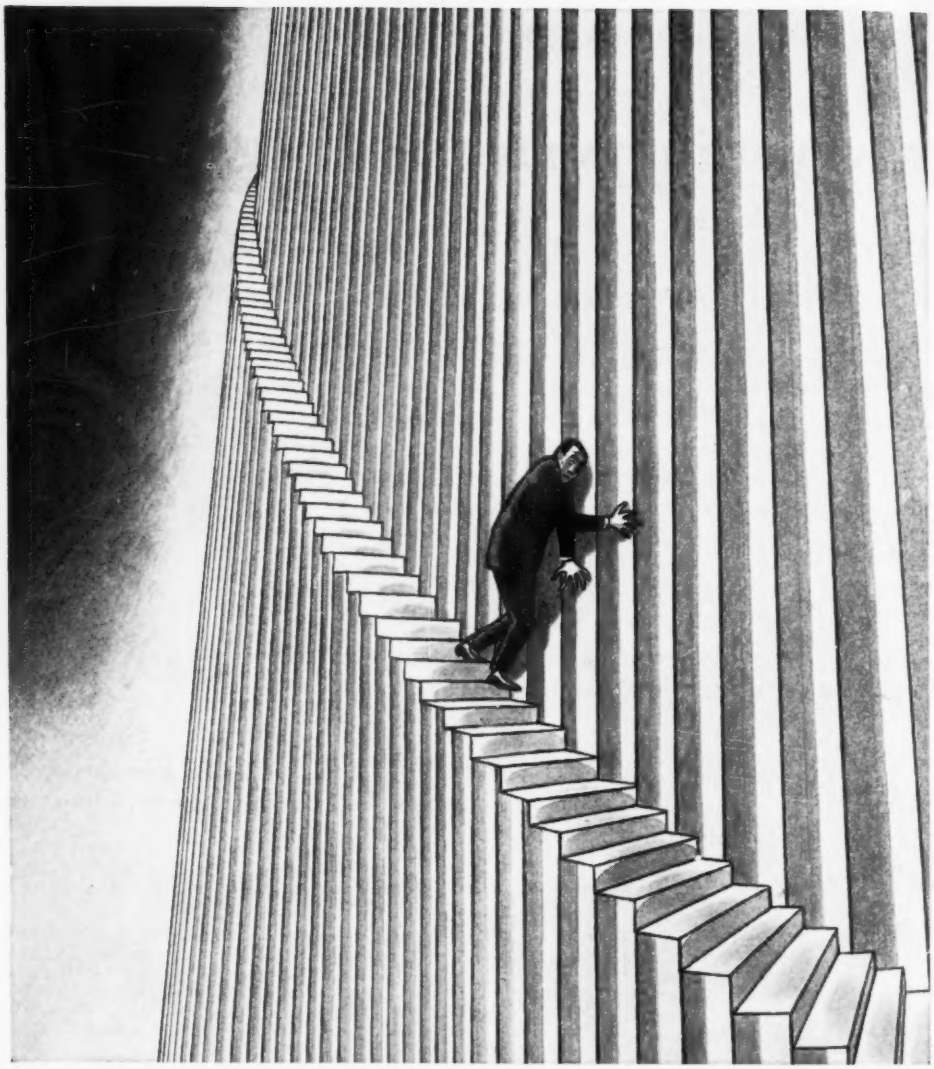
"Of particular interest has been the virtual absence of constipation despite adequate blood pressure control. This finding suggests a lower risk of paralytic ileus. . . ."[1]

Supplied: Tablets, scored, 20 and 40 mg., vials of 100.

1. Dunsmore, R.A., et al.: Am. J. M. Sc. *236*:483 (Oct.) 1958. 2. Blaquier, P., et al.: Univ. Michigan M. Bull. *24*:409 (Oct.) 1958. 3. Smirk, F.H.: Submitted for publication. 4. Janney, J.F.: Submitted for publication. 5. Council on Drugs, A.M.A.: J.A.M.A. *166*:640 (Feb. 8) 1958. 6. Freis, E.D., and Wilson, I.M.: Circulation *13*:856 (June) 1956. 7. Moyer, J.H., et al.: A.M.A. Arch. Int. Med. *98*:187 (Aug.) 1956. 8. Moyer, J.H., et al.: Am. Pract. & Dig. Treat. *7*:1765 (Nov.) 1956. 9. Dunsmore, R.A. In Tislow, R.F., et al.: Scientific Exhibit. Presented at Annual Convention of A.M.A., San Francisco, June 23-27, 1958.

...tensin®

Ganglionic blockade with fewer and milder by-effects



The nightmare of hypoglycemia

It can happen, almost without warning, to many diabetics on insulin. One moment, the patient appears normal; the next, he goes into a state of hypoglycemia, perhaps even shock. For some it is a terrifying threat with which to live.

But for many of these patients there is a rational alternative: *oral* management. On Orinase,* control is smoother, blood sugar levels are more steady – and the terror is dispelled. Some brittle diabetics are "stabilized" on combined Orinase-insulin therapy.

For *all* your responsive patients on Orinase, there is the assurance of better control and easier patterns of living. *TRADEMARK, REG. U. S. PAT. OFF. — TOLBUTAMIDE, UPJOHN

THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

Upjohn **ORINASE**

for the tense and nervous patient

relief comes fast and comfortably

–does not produce autonomic side reactions
–does not impair mental efficiency, motor control, or normal behavior.

Usual Dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*—400 mg. *unmarked,* coated tablets.

Miltown®

meprobamate (Wallace)

WALLACE LABORATORIES / *New Brunswick, N. J.*

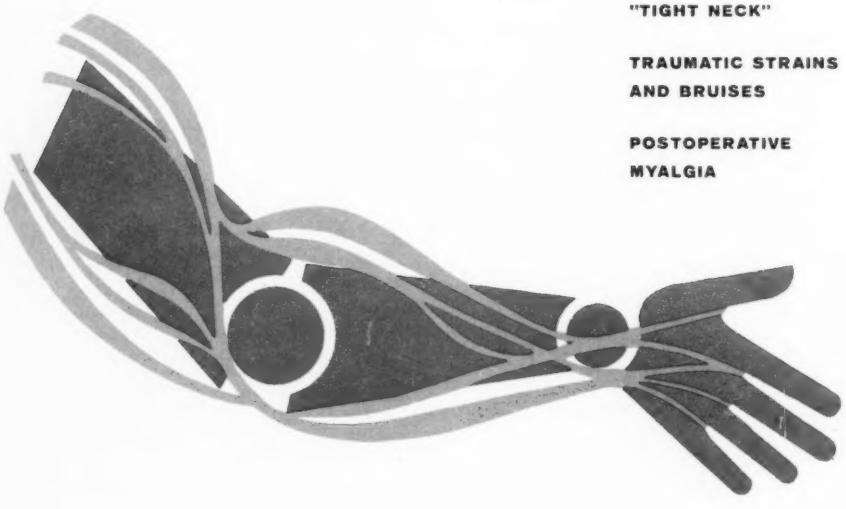
CM-9470

NOW

. . . a new way to relieve pain and stiffness in muscles and joints

indicated in:

- MUSCLE STIFFNESS
- LUMBOSACRAL STRAIN
- SACROILIAC STRAIN
- WHIPLASH INJURY
- BURSITIS
- SPRAINS
- TENOSYNOVITIS
- FIBROSITIS
- FIBROMYOSITIS
- LOW BACK PAIN
- DISC SYNDROME
- SPRAINED BACK
- "TIGHT NECK"
- TRAUMATIC STRAINS AND BRUISES
- POSTOPERATIVE MYALGIA



Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain ■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids

■ More effective than muscle relaxants

SOMA has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with previously used analgesic, sedative or relaxant drugs.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

ACTS FAST. Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

NOTABLY SAFE. Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy, particularly on high dosage.

EASY TO USE. Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

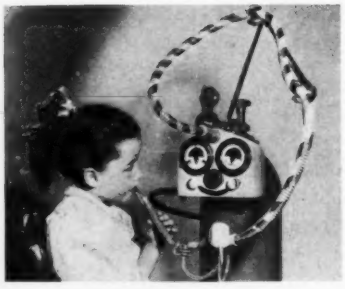
SUPPLIED: Bottles of 50 white coated 350 mg. tablets.

Literature and samples on request.

WALLACE LABORATORIES, NEW BRUNSWICK, N. J.

New *for your armamentarium*

Information published in this department is supplied by the manufacturers of the products described.



• PEDIATRIC VENTALUNG

DESCRIPTION: Designed for children as young as one year old, this instrument is patterned after intermittent positive-pressure breathing devices for adults. It has a flow rate which is one-half the volume required for an adult. The apparatus relieves severe lung congestion, ventilates the lungs, and nebulizes drugs, either for inspiration or continuously. The control box is designed like a clown's face. The clown's rolling eye is the pressure gauge and his red nose is the emergency button, which begins artificial respiration or allows manual operation of the breathing cycle. The unit can be used with mouthpiece, mask or tracheotomy tube and with either cylinder or piped oxygen.
PRODUCER: National Cylinder Gas Division of Chemetron Corporation, Chicago.

• EFFERSYLLIUM

PURPOSE: Bulk laxative.
COMPOSITION: Psyllium hydrocolloid, sucrose, potassium bicarbonate, citric acid and artificial sweeteners.
DOSAGE AND ADMINISTRATION: For adults, 1 rounded teaspoonful in a glass of water one to three times daily; for children, as prescribed.
HOW SUPPLIED: 9 oz. bottles.
PRODUCER: The Stuart Company, Pasadena, Calif.

• DARVO-TRAN®

PURPOSE: Analgesic with tranquilizing action.
COMPOSITION: Each PULVULE® contains:

Dextro propoxyphene hydrochloride (DARVON®)	32 mg.
Acetylsalicylic acid (A.S.A.®)	325 mg.
Phenaglycodol (ULTRAN®)	150 mg.

INDICATIONS FOR USE: Tension headache, whiplash injuries, skeletal muscle discomfort, low back and moderate postoperative pain, postpartum discomfort, and arthritis.
DOSAGE AND ADMINISTRATION: Usual adult dosage is 1 Pulvule three or four times a day; for severe pain, 2 Pulvules three or four times daily.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Eli Lilly and Company, Indianapolis.

(Continued on page A-138)

in Turkey,
it's called the 'Turkey trot'

diarrhea by any name

GASTROENTERITIS
BACILLARY DYSENTERY
PARADYSENTERY
SALMONELLOSIS
DIARRHEA OF THE NEWBORN
NONSPECIFIC DIARRHEA
"SUMMER COMPLAINT"

usually responds rapidly to

Cremomycin®

NEOMYCIN-SULFASUXIDINE®-KAOLIN-PECTIN SUSPENSION

for *rapid* relief of virtually all diarrheas

fruit-flavored, readily accepted by patients of all ages*

Neomycin—rapidly bactericidal against most intestinal pathogens, but is relatively ineffective against such diarrhea-causing organisms as Shigella.

SULFASUXIDINE®—an ideal adjunct to neomycin because it is highly effective against Shigella and certain other neomycin-resistant organisms.

Kaolin and Pectin—coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

***For infants, CREMOMYCIN may be administered in the regular bottle feeding since its fine particles easily pass through a standard nursing nipple.**

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILA. 1, PA.

CREMOMYCIN AND SULFASUXIDINE (SUCCINYLSULFATHIAZOLE) ARE TRADEMARKS OF MERCK & CO., INC.

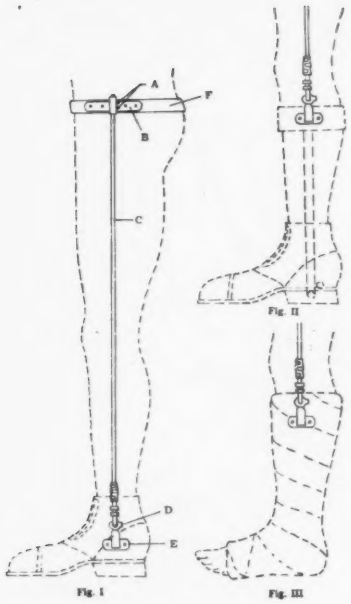


Fig. I

Fig. II

Fig. III

• MILLER TWISTER

DESCRIPTION: Flexible and lightweight, this support places and holds legs in proper position for ambulation. Hip rotation is controlled without limitation of the functional motion of knee and ankle joints.
PRODUCER: Rehabilitation Products, division of American Hospital Supply Corporation, Evanston, Ill.

• NORISODRINE® SYRUP
(New Product Form)

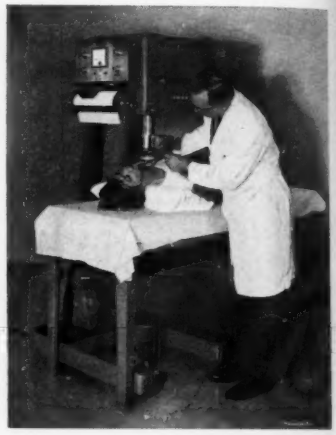
PURPOSE: Bronchodilator and expectorant.
COMPOSITION: Each 30 ml. of syrup contains:

Norisodrine sulfate (isoproterenol sulfate)	18 mg.
Calcium iodide (anhydrous)	900 mg.
Alcohol	6%

CAUTION: Overdosage may result in dizziness, palpitation, nervousness and tachycardia. The drug should not be given to patients with a history of intolerance to iodides; it should be administered with caution to patients with hypertension or other cardiovascular disease.
DOSAGE AND ADMINISTRATION: Usual adult dosage is 1 teaspoonful four times a day, or as directed.
HOW SUPPLIED: 1 pint bottles.
PRODUCER: Abbott Laboratories, North Chicago.

• INJECTION DECADRON® PHOSPHATE
(New Product Form)

PURPOSE: Corticosteroid therapy.
COMPOSITION: Dexamethasone 21-phosphate (4 mg. per cubic centimeter).
DOSAGE AND ADMINISTRATION: Intravenously, intramuscularly, intrasynovially or in soft tissues.
HOW SUPPLIED: 5 cc. vials.
PRODUCER: Merck Sharp & Dohme, division of Merck & Co., Inc., Philadelphia.



• CLINISCANNER

DESCRIPTION: Providing highly defined scans while subjecting the patient to smaller doses of radiation, this scintillation scanner scans an area 11 by 14 in. A contrast circuit makes it possible to emphasize small relative differences in radioisotope concentration and to minimize the effect of background radiation on the scan. Reading of scattered radiation is eliminated by a pulse-height analyzer that records only the peak energy of the selected isotope. Halo is eliminated by a 3 in. lead detector shield, which also contributes to reducing background and improving collimation. Motor-driven for vertical and horizontal travel, the unit may be set up on a mobile floor mast or mounted on a wall bracket. A light beam from the center of the collimator accurately aligns the scan to the patient. The scanner also may be used for uptake measurements with the use of a flat field collimator.
PRODUCER: Picker X-Ray Corporation, White Plains, N.Y.

(Continued on page A-140)

For your ambulant asthmatic . . . **"Air in a hurry!"**

Nephenalin®, the square purple tablet that relieves asthma with nebulizer speed for 4 full hours, offers convenience and reassurance to your ambulant asthmatic patient. Placed under the tongue, the NEPHENALIN tablet quickly releases 10 mg. of Isoproterenol HCl, the potent homologue of epinephrine, for immediate opening of the airway. Swallowed, the NEPHENALIN tablet provides theophylline (2 gr.), ephedrine (3/8 gr.) and phenobarbital (1/8 gr.), for sustained protection from asthmatic seizure. NEPHENALIN is available for your prescription in bottles of 50 and 100 tablets. Also available: NEPHENALIN PEDIATRIC. *Thos. Leeming & Co. Inc.* NEW YORK 17, N.Y.

• **PROPORTIONAL COUNTER CONVERTER**

DESCRIPTION: An all-purpose instrument for measuring alpha, beta and gamma radiation, this unit converts any scaler with a variable high-voltage supply into a proportional counting system. The converter connects to the GM input of the scaler and plugs into a 110 V circuit. Samples are counted inside a gas-flow chamber that yields full 2 π geometry. Every alpha and beta ray emitted into the chamber is counted; the unit discriminates between them at the high-voltage setting only. The converter is available in three styles and is equipped with a low-voltage power supply, gas-flow control, and a completely transistorized amplifier-discriminator.
PRODUCER: Nuclear Measurements Corporation, Indianapolis.

• **ILOSONE® LAURYL SULFATE SUSPENSION AND DROPS**
(New Product Forms)

DESCRIPTION: This antibiotic (propionyl erythromycin ester lauryl sulfate) is now available in oral suspension and drops. When water is added as directed, each 5 cc. of the suspension provides activity equivalent to that of 125 mg. of erythromycin base, and each drop provides activity equal to that of 5 mg. of erythromycin base.
DOSAGE AND ADMINISTRATION: Usual dosage for adults and for children weighing more than 50 lb., 250 mg. every six hours; in more severe infections, 500 mg. every six hours; in overwhelming infections, 1 gm. every six hours. Dosage for children is determined according to the weight of the patient.
HOW SUPPLIED: Suspension in 60 cc. bottles; drops in 10 cc. bottles with calibrated droppers.
PRODUCER: Eli Lilly and Company, Indianapolis.

• **DURABOLIN®**

PURPOSE: Tissue-building stimulant.
COMPOSITION: Nandrolone phenpropionate.
INDICATIONS FOR USE: Asthenia, before and after surgery, during corticosteroid therapy, conditions of faulty calcium balance, retarded growth and development in children, uremia, and inoperable cancer.
DOSAGE AND ADMINISTRATION: For adults, 25 mg. (1 cc.) intramuscularly once a week or 50 mg. every second week; for children, 12.5 mg. (0.5 cc.) intramuscularly once a week or 25 mg. every second week.
HOW SUPPLIED: 1 cc. ampules in boxes of three; 5 cc. vials.
PRODUCER: Organon, Inc., Orange, N. J.

• **LOTIOBLANC**
(New Package Form)

DESCRIPTION: A combination of zinc sulfate and sulfurated potash used to treat acne, this product is now available in 2 oz. plastic bottles.
PRODUCER: Arnar-Stone Laboratories, Inc., Mount Prospect, Ill.

• **LITE-RITE SHOE TESTER**

DESCRIPTION: Providing a sure means of testing static-charge conductivity of footwear, this device may be placed outside operating rooms and plugged into an ordinary AC circuit. When a person steps onto the two metal plates of the unit, a light indicates a satisfactory amount of resistance. The light remains off if there is a resistance of more than 1,000,000 ohms, in which case the shoes must be cleaned and retested. Test buttons indicate that the unit is in working order and is properly calibrated.
PRODUCER: National Cylinder Gas Division of Chemetron Corporation, Chicago.

(Continued on page A-142)

UNSURPASSED

UNSURPASSED

UNSURPASSED

UNSURPASSED

HP* ACTHAR *Gel*

unsurpassed in ACTH therapy

The most extensive clinical and experimental background.

The most widely used in practice.

With a documented record of safety not matched by any other drug of comparable action, scope and efficacy.

And a therapeutic effect of rapid onset, lasting up to 72 hours.

HP* ACTHAR® *Gel* is fluid at room temperature and as convenient to inject as any other aqueous preparation.

HP* ACTHAR *Gel* is the Armour Pharmaceutical Company brand of Purified Repository Corticotropin (ACTH).

Available in 5 cc. vials of 20, 40, 80 U.S.P. Units/cc. Also in a disposable syringe form, in a potency of 40 U.S.P. Units.

*Highly Purified

ARMOUR PHARMACEUTICAL COMPANY

KANKAKEE, ILLINOIS

Armour Means Protection

© 1959, A. P. Co.

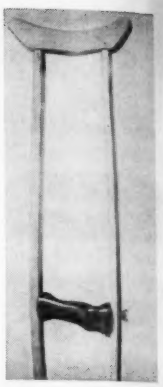
• OXYGEN THERAPY AND RESUSCITATION UNIT (Model 901)

DESCRIPTION: Designed to provide oxygen therapy and positive-pressure resuscitation for small domesticated animals, this unit features a transparent, cone-shaped mask of TENITE® butyrate plastic. Rubber rims on the mask assure comfort and adequate coverage and seal. The unit includes large and small face masks, an inhaler assembly and a nonrebreathing bag.
PRODUCER: Ohio Chemical & Surgical Equipment Co. (A division of Air Reduction Company, Inc.), Madison, Wis.

• MINOMETER (Model 687)

DESCRIPTION: Portable and fully transistorized, this instrument features high-visibility readout of indirect-reading pocket dosimeters and stray radiation chambers. The 4 in. mirrored and illuminated scale has range settings of 0 to 20 μr. and 0 to 200 μr. The unit can be used with or without film badges, and it gives an immediate indication of the dosage to which personnel have been subjected. There is no delay caused by processing.
PRODUCER: Victoreen Instrument Company, Cleveland.

• CRUTCH GRIP



DESCRIPTION: Designed to reduce fatigue, this crutch grip conforms to the natural angle of the hand and may be used by persons whose hands are limited in function. Constructed of neutral-colored plastic, the grip is resilient, requires no padding, does not absorb perspiration or odor, and is easily cleaned with soap and water. It is available in either a standard or a large size. The standard-sized grip adapts to all standard crutches with presently used wing nut and bolt connections; the large-sized grip is supplied with a wing nut and bolt.
PRODUCER: J-Line Products, Minneapolis.

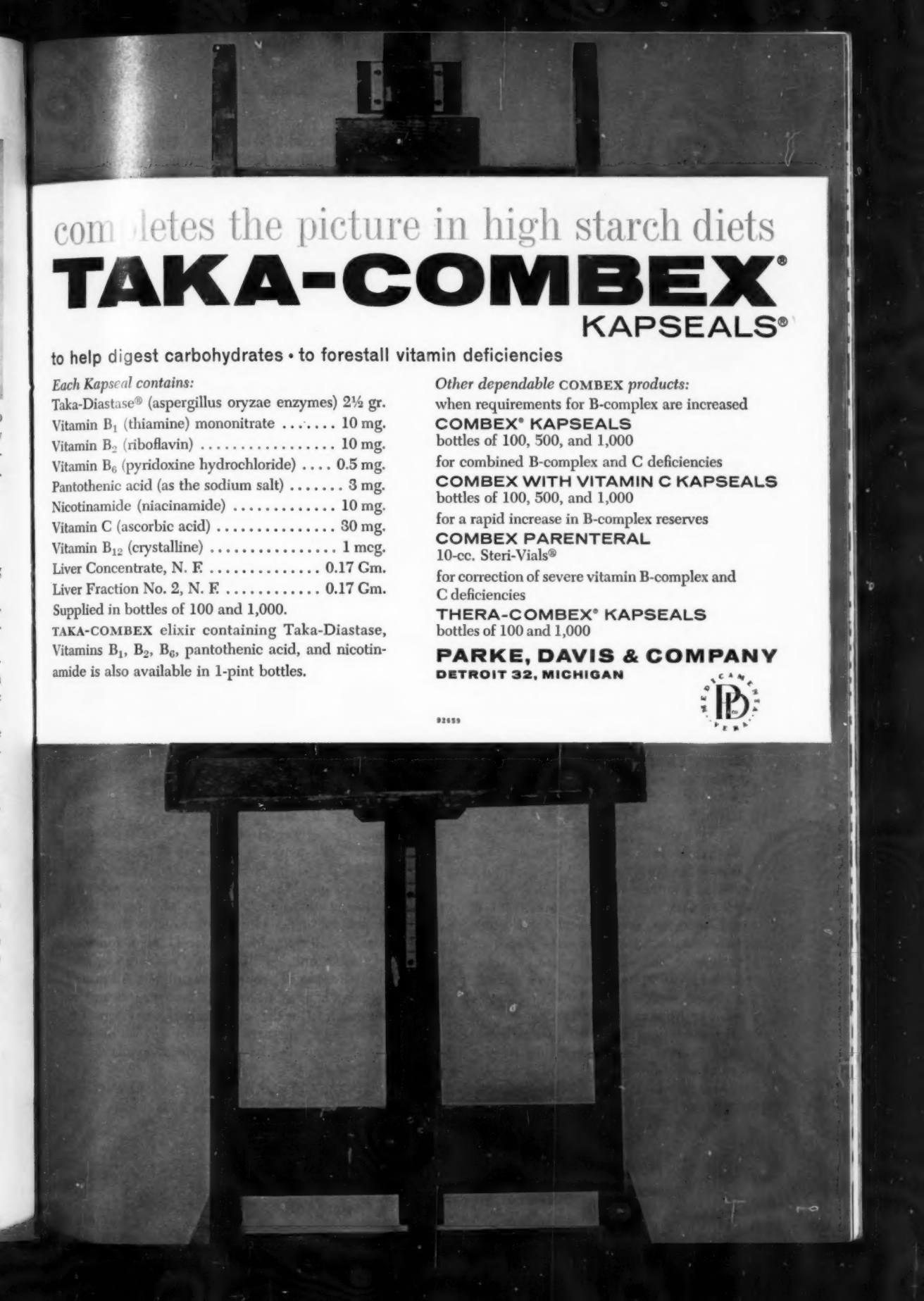
• TRALCYON® FILMTAB®

PURPOSE: Anticholinergic and tranquilizing action.
COMPOSITION: Each Filmtab contains 25 mg. hexocylium methylsulfate (TRAL®) and 300 mg. ectylurea (2-ethyl-*cis*-crotonylurea).
CAUTION: Contraindicated in patients with glaucoma or pyloric stenosis; should be used with special caution in patients with serious cardiac disease or prostatic hypertrophy.
DOSAGE AND ADMINISTRATION: Usual adult dosage is 1 Filmtab four times daily, adjusted according to patient's response.
HOW SUPPLIED: Bottles of 50 and 500.
PRODUCER: Abbott Laboratories, North Chicago.

• ENFAMIL

DESCRIPTION: This infant formula has a protein level approximating that of human milk. It also contains a high percentage of unsaturated fatty acids, 12 essential vitamins, minerals, and lactose as the carbohydrate. The zero curd tension of the formula provides protein digestibility, and a low osmotic concentration protects the kidneys from excessive excretion and solution load.
HOW SUPPLIED: Enfamil liquid in 13 oz. cans; Enfamil powder in 1 lb. cans with measure.
PRODUCER: Mead Johnson & Company, Evansville, Ind.

(Continued on page A-144)



completes the picture in high starch diets

TAKA-COMBEX®

KAPSEALS®

to help digest carbohydrates • to forestall vitamin deficiencies

Each Kapseal contains:

Taka-Diastase® (aspergillus oryzae enzymes) 2½ gr.
Vitamin B_1 (thiamine) mononitrate ..... 10 mg.
Vitamin B_2 (riboflavin) ..... 10 mg.
Vitamin B_6 (pyridoxine hydrochloride) .... 0.5 mg.
Pantothenic acid (as the sodium salt) ..... 3 mg.
Nicotinamide (niacinamide) ..... 10 mg.
Vitamin C (ascorbic acid) ..... 30 mg.
Vitamin B_{12} (crystalline) ..... 1 mcg.
Liver Concentrate, N. F. ..... 0.17 Gm.
Liver Fraction No. 2, N. F. ..... 0.17 Gm.

Supplied in bottles of 100 and 1,000.

TAKA-COMBEX elixir containing Taka-Diastase, Vitamins B_1, B_2, B_6, pantothenic acid, and nicotinamide is also available in 1-pint bottles.

Other dependable COMBEX *products:*

when requirements for B-complex are increased

COMBEX® KAPSEALS
bottles of 100, 500, and 1,000

for combined B-complex and C deficiencies

COMBEX WITH VITAMIN C KAPSEALS
bottles of 100, 500, and 1,000

for a rapid increase in B-complex reserves

COMBEX PARENTERAL
10-cc. Steri-Vials®

for correction of severe vitamin B-complex and C deficiencies

THERA-COMBEX® KAPSEALS
bottles of 100 and 1,000

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

92659

• **LITTLE SCOT WHEEL CHAIR**

DESCRIPTION: Designed for children aged two to seven, this folding wheel chair provides ease and freedom of movement. The chassis absorbs shocks and keeps the 20 in. tangent-spoked wheels in contact with the floor. Hidden "X" members provide rigid support and easy folding action. The arm design permits close approach to desk or table, and the aluminum folding footrests are adjustable. The chair has a lightweight tubular steel frame and brown, washable slip-on upholstery. Rod-reinforced aluminum skirt guards are an additional feature.
PRODUCER: Rehabilitation Products, division of American Hospital Supply Corp., Evanston, Ill.

• **XYLOCAINE® HYDROCHLORIDE 4%**
(New Product Form)

PURPOSE: Local anesthetic for topical use and for transtracheal and retrobulbar injection.
COMPOSITION: Each cubic centimeter contains:

Diethylaminoacet-2,6-xylidide (Xylocaine hydrochloride)	0.04 gm.
Methylparaben	0.001 gm.
Water for injection	q.s. ad 1 cc.

CAUTION: Absolute contraindications are traumatized mucosa, sepsis in the region of the proposed injection, severe shock, and heart block. Relative contraindications are septicemia, severe hypertension and extreme youth.
DOSAGE AND ADMINISTRATION: Average adult dose for topical anesthesia is 1 to 5 cc. applied with a swab or by spraying or instillation; for retrobulbar anesthesia, 3 to 7 cc. injected retrobulbarly and around the upper trunks of the facial nerve. For children and debilitated and aged patients, the dosages should be proportionately reduced.
HOW SUPPLIED: 5 cc. color-break ampules in cartons of 10; 50 cc. bottles for topical use only.
PRODUCER: Astra Pharmaceutical Products, Inc., Worcester, Mass.

• **TRAL® GRADUMET®, 75 MG.**
(New Dosage Form)

DESCRIPTION: Primarily to control nighttime secretion in patients with peptic ulcer, this product provides anticholinergic action for a period of up to 12 hours.
CAUTION: Contraindicated in the presence of glaucoma and pyloric stenosis; should be used with caution in patients with serious cardiac disease or prostatic hypertrophy.
DOSAGE AND ADMINISTRATION: For adults, 1 Gradumet at bedtime.
HOW SUPPLIED: 75 mg. Gradumets in bottles of 50 and 500.
PRODUCER: Abbott Laboratories, North Chicago.

• **THERMOPHIL ELECTRONIC THERMOMETER**

DESCRIPTION: Stabilized against drift, this thermometer registers from 200° C. to more than 450° C. Response is given at 0.75 second in liquids, 2.2 seconds on surfaces. Operating on 115 V or batteries, the thermometer provides exactitude to within ± 0.33 to 0.67 per cent. A breakdown of the range into three or four overlapping scales provides 8½ or 11½ in. full-scale length for fine legibility with wide range. One hundred types of probes are available. All probes are interchangeable between instruments in this line which cover the same temperature range. The thermometer measures 7 by 5 by 2¼ in. and has a leather carrying case and straps available for field use.
PRODUCER: Chicago Apparatus Co., Chicago.

(Continued on page A-146)

In skeletal-muscle disabilities . . .

Curbs spasm, relieves rigidity, and relaxes psychic tension

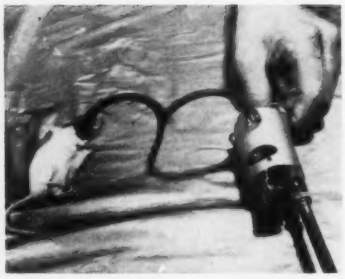
Of all muscle relaxants in current use, only meprobamate is supported by hundreds of published clinical studies that demonstrate relaxing action on both the brain and the skeletal musculature. EQUANIL reduces muscular spasm and tension, aids in the restoration of mobility, speeds rehabilitation, lessens the emotional overlay.

Prescribe it in spasm or tension secondary to: sprains, strains, contractures, fibrositis, myositis, low-back syndrome, frozen shoulder, cervical-rib syndrome, herniated intervertebral disk, wryneck, rheumatoid arthritis, rheumatoid or traumatic spondylitis, certain neuromuscular disorders.

Equanil®

Meprobamate, Wyeth

Wyeth® Philadelphia 1, Pa.



• HANDY OB RESUSCITATOR

DESCRIPTION: Especially designed for resuscitation of newborns, this unit is sufficiently sensitive to force air through an opening the size of a pinhole. Precision controls automatically adjust the flow of oxygen according to the capacity of the lungs. A mask slightly larger than a 50 cent piece fits snugly over the baby's face, or oxygen may be administered through a tube inserted into the throat. After the passageway is cleared, the instrument can be switched to inhalation operation. The 7½ oz. cylindrical mechanism is 3 in. long and 2 in. in diameter.
PRODUCER: National Cylinder Gas Division of Chemetron Corporation, Chicago.

• MIDICEL® ACETYL SUSPENSION
(New Product Form)

PURPOSE: Treatment of infections responsive to sulfonamide therapy.
COMPOSITION: Each 5 cc. suspension is equivalent to 250 mg. Midicel.
DOSAGE AND ADMINISTRATION: Usual adult dosage, 4 teaspoonfuls (1 gm.) the first day, followed by 2 teaspoonfuls daily thereafter. Dosage for children is based on body weight.
HOW SUPPLIED: 4 oz. bottles.
PRODUCER: Parke, Davis & Company, Detroit.

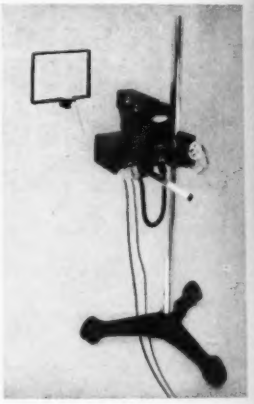
• PANTHOJECT

PURPOSE: To restore normal intestinal motility in patients requiring intra-abdominal surgery.
COMPOSITION: 250 mg. d, calcium pantothenate per cubic centimeter.
INDICATIONS FOR USE: Prevention and correction of paralytic ileus, postoperative abdominal distention, intestinal atony, and retention of flatus and feces.
DOSAGE AND ADMINISTRATION: 1 cc. injected intramuscularly before or immediately following intra-abdominal surgery, or both. Repeat every six hours until normal intestinal motility is restored.
HOW SUPPLIED: 10 cc. multiple-dose vials in boxes of six.
PRODUCER: U. S. Vitamin & Pharmaceutical Corp., New York.

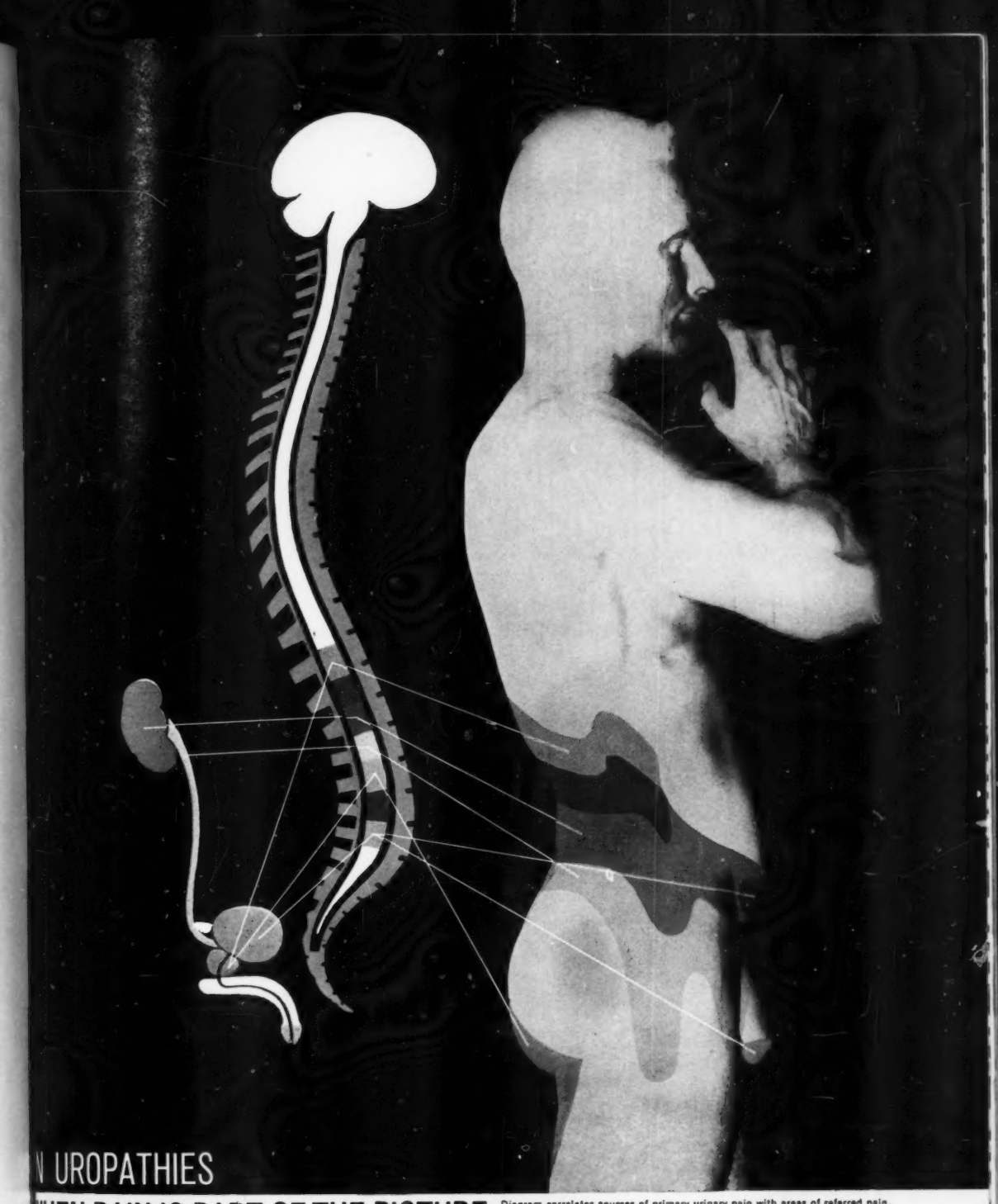
• ROLL FILM PROCESSOR

DESCRIPTION: With this unit, 8, 16, 35 and 70 mm. cinefilm can be developed almost immediately. The processor also develops photofluorographic film from chest x-ray units and will process film in any length up to 100 ft. The unit measures 15 in. by 3½ ft. and can be rolled easily to any place desired. It operates on an ordinary AC outlet and requires a sink for water supply and drain.
PRODUCER: Picker X-Ray Corporation, White Plains, N.Y.

• CINERAY MOTION-PICTURE SYSTEM



DESCRIPTION: Compactly designed, this portable motion-picture system produces bright, sharp 16 mm. cinefluorographic pictures in either standard or slow motion. All or any portion of a standard 12 by 15 in. fluoroscope screen can be photographed, and pictures may be used for extended study and diagnosis. There are minimal sequelae from radiation exposure when usual precautions are observed. Patients need be exposed for only three seconds while a film loop is taken. The operator may be completely isolated from radiation when Cineray remote controls are used.
PRODUCER: American Teletronics Inc., Anaheim, Calif.



N UROPATHIES

WHEN PAIN IS PART OF THE PICTURE

rinary tract pain, at the source or referred, is subject to the rapid
algesic action of the azo dye in Azo Gantrisin. Azo Gantrisin combines
ramatic relief of symptoms with proven effective action against infec-
ons carried by either blood stream or urine.
luable also following urologic manipulation and surgery.

AZO GANTRISIN

NTRISIN®—brand of sulfisoxazole ROCHE®

Diagram correlates sources of primary urinary pain with areas of referred pain.

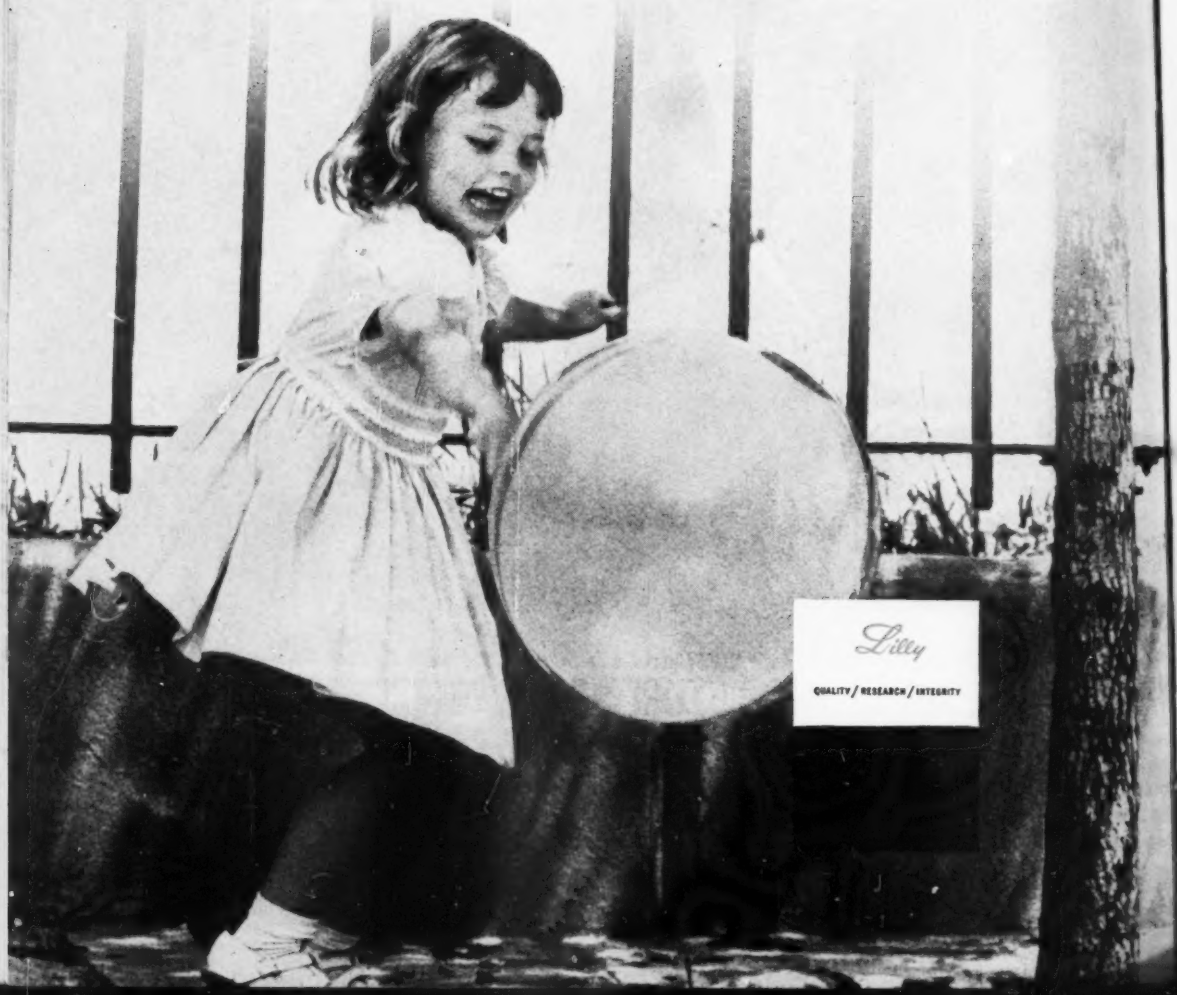
Dosage: Adults—2 tablets four times daily.
Children under 100 lbs—1 tablet four times daily.
Each tablet provides 0.5 Gm Gantrisin plus 50 mg phenylazodiamino-pyridine HCl—bottles of 100 and 500.

ROCHE
LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley 10, N. J.

NOW ILOSONE® WORKS

(propionyl erythromycin ester, Lilly)

FOR CHILDREN TOO!



NEW

ILOSONE® 125

LAURYL SULFATE

SUSPENSION

(propionyl erythromycin ester lauryl sulfate, Lilly)

Deliciously flavored • Decisively effective • Exceptionally safe

FORMULA

Each 5-cc. teaspoonful provides Ilosone Lauryl Sulfate equivalent to 125 mg. erythromycin base activity.

USUAL DOSAGE

10 to 25 pounds	5 mg. per pound of body weight	every six hours
25 to 50 pounds	1 teaspoonful	
Over 50 pounds	2 teaspoonfuls	

In more severe infections, these dosages may be doubled.

SUPPLIED in bottles of 60 cc.

NEW! ILOSONE DROPS

LAURYL SULFATE

Formula: Each drop provides Ilosone Lauryl Sulfate equivalent to 5 mg. erythromycin base activity.

Supplied in bottles of 10 cc.

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

first in preference for relief from cough

quiets the cough and calms the patient

Expectorant
Antihistaminic

Sedative
Topical anesthetic

PHENERGAN®

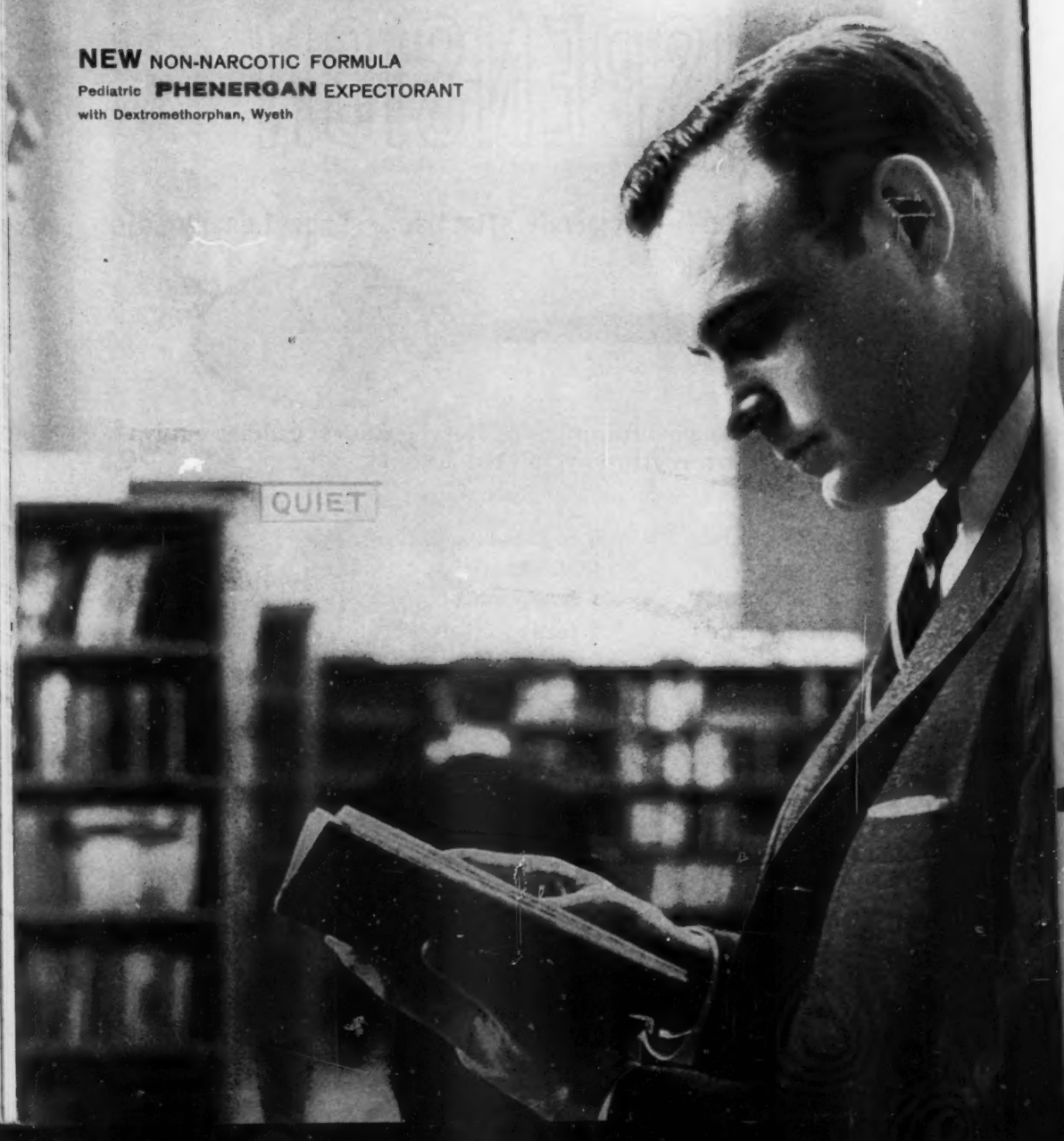
EXPECTORANT

Promethazine Expectorant, Wyeth
with Codeine

Plain (without Codeine)

Wyeth®
Philadelphia 1, Pa.

NEW NON-NARCOTIC FORMULA
Pediatric PHENERGAN EXPECTORANT
with Dextromethorphan, Wyeth



QUESTIONS ON THE CLINICAL USE OF KANTREX

Q Why should I use KANTREX® Injection* when there are so many other antibiotics available?

A

Because KANTREX Injection is bactericidal to a wide variety of organisms, including many that are highly resistant to the other antibiotics[3,4,10,12,13,17,18,20,21,23,24,25,27,30,33,35,37]

—organisms such as *Staph. aureus, Staph. albus, A. aerogenes, E. coli, H. pertussis, K. pneumoniae, Neisseria* sp., *Shigella, Salmonella* and many strains of *B. proteus.*

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

Next page, please . . . . . .

* Kanamycin sulfate injection (Bristol)

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

A A very good question, but it is reassuring to note that in almost two years of clinical use of KANTREX for the treatment of infections for which it is recommended, the emergence of KANTREX-resistant bacterial populations has not been a problem.

Q *My impression is that* KANTREX *is just another neomycin. Isn't that so?*

A Indeed not. The only thing KANTREX and neomycin have in common is a similar antimicrobial spectrum. Otherwise, they're very different: they have different chemical structures; the toxicity of KANTREX is "much less than that of neomycin"[14]; and clinically, KANTREX Injection is practical for systemic administration routinely, while neomycin is not.

Q *You mean that* KANTREX *Injection doesn't have the nephrotoxicity of neomycin?*

A Precisely. It's true that when KANTREX Injection is used, urinary casts – even slight albuminuria or microscopic hematuria – may appear, especially in poorly hydrated patients, but this does not reflect any progressive damage to the kidneys. These signs promptly disappear on adequate hydration or termination of therapy.

Q *Then why do you recommend reduced dosage in patients with renal impairment?*

A Because renal impairment causes an excessive accumulation of KANTREX in the blood and tissues, when usual doses are administered. Since KANTREX Injection is excreted entirely by the kidneys, renal impairment leads

to unnecessarily high and prolonged blood levels; and such excessive concentrations increase the risk of ototoxicity.

Q *Is that why we see reports of patients developing hearing loss during* KANTREX *Injection therapy?*

A Yes. A study of the few reported cases in which patients have suffered impaired hearing will show that in every instance they had pre-existing or concurrent renal impairment, yet received usual or excessive doses of KANTREX Injection. Dosage recommendations for KANTREX Injection emphasize that in patients with renal dysfunction, adequate serum levels can be achieved with a fraction of the dose suggested for patients with normal kidney function – with minimal risk of ototoxicity.

Q *Since urinary tract infections are often accompanied by renal impairment, does that mean I shouldn't use* KANTREX *Injection in such conditions?*

A Not at all. With proper precautions, KANTREX Injection is an excellent drug for the treatment of urinary tract infections, especially those due to *Proteus, A. aerogenes* and *E. coli*, even when renal impairment is present.

Q *What are the "proper precautions" in a patient with impaired renal function?*

A The package literature covers them in detail. First, the daily dose should be reduced in such a patient. Then, if he is going to receive KANTREX Injection for 7 days or more, a pre-treatment audiogram should be done, and it should be repeated at appropriate intervals during therapy. If tinnitus or subjective hearing loss develops, or if followup audiograms show significant loss of high frequency response, KANTREX therapy should be discontinued. However, therapy for 7 days or more

is seldom required because the clinical response to KANTREX Injection is so rapid.

Q *Why do you put so much emphasis on* KANTREX'S *"rapid action"? Every antibiotic I've heard about is supposed to be "rapid acting."*

A There is such an abundance of clinical evidence about "rapid acting" that it takes KANTREX Injection out of the "supposed-to" class.[1,2,3,7,8,9,11,15,16,19,21,22,26,29,32,33] Remember, the effectiveness of KANTREX Injection therapy can usually be appraised in 24 to 36 hours. That's definite evidence of rapid action. In fact, one group of investigators reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."[29]

Q *Does* KANTREX *Injection cause blood dyscrasias?*

A In extensive clinical and toxicity studies by numerous investigators, as well as almost two years of general use, not a single instance of such toxicity has been reported.

Q *Can I administer* KANTREX *Injection in any other way than by the intramuscular route?*

A Yes. While it's usually given intramuscularly, other routes are practicable: intravenous, intraperitoneal, by aerosol, and as an irrigating solution. Complete instructions are included in the package insert.

Q *So you think I ought to use* KANTREX *Injection as my first choice antibiotic in staph and gram-negative infections?*

A Yes – because all evidence to date indicates that it is bactericidal against a wide range of organisms... rapid acting... does not encourage development of bacterial resistance... is well tolerated in specified dosage... and has not caused any blood dyscrasias.

KANTREX® CAPSULES

for local gastrointestinal therapy... not for systemic infections

Q *Why can't I use* KANTREX *Capsules for systemic medication?*

A Because there is only negligible absorption of KANTREX from the gastrointestinal tract.[3,5,6,8,28,34] Thus, capsules cannot provide effective blood levels.

Q *Then what are* KANTREX *Capsules used for?*

A Preoperative bowel sterilization, and local treatment of intestinal infections due to kanamycin-sensitive organisms.

Q *I've been using neomycin for preoperative bowel sterilization. Why should I switch to* KANTREX *Capsules?*

A Because KANTREX has been rated as "superior to neomycin" for this purpose.[6] It provides rapid and satisfactory control of coliforms, clostridia, staphylococci and streptococci; yeasts do not proliferate; stool concentrations of the drug are exceptionally high; and nausea, vomiting or intestinal irritation have not been observed.[5,6]

Q *What advantages do* KANTREX *Capsules offer me in the treatment of intestinal infections?*

A A high degree of effectiveness against most of the pathogens responsible for such infections: *Salmonella, Shigella, Staph. aureus, E. coli* and *Endamoeba histolytica.* Moreover, their use has been "remarkably free of any side effects."[31]

KANTREX®

INJECTION KANAMYCIN SULFATE INJECTION

INDICATIONS

Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives": genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis.

DOSAGE: INTRAMUSCULAR ROUTE

Recommended daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses.

For intramuscular administration, KANTREX Injection should be injected deeply into the upper outer quadrant of the gluteal muscle.

TOXICITY

When the recommended precautions are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of ototoxic reactions is negligible.

In patients with renal disease and impaired renal function, the daily dose of KANTREX should be reduced in proportion to the degree of impairment to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 7 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

OTHER ROUTES OF ADMINISTRATION

KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

PRECAUTIONS

Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

SUPPLY

Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.
KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

CAPSULES (for local gastrointestinal therapy; not for systemic medication)

INDICATIONS AND DOSAGE

For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

For intestinal infections: Adults: 3.0 to 4.0 Gm. (6 to 8 capsules) per day in divided doses for 5 to 7 days. Infants and children: 50 mg. per kg. per day in 4 to 6 divided doses for 5 to 7 days.

PRECAUTION

Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

SUPPLY

KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

REFERENCES:

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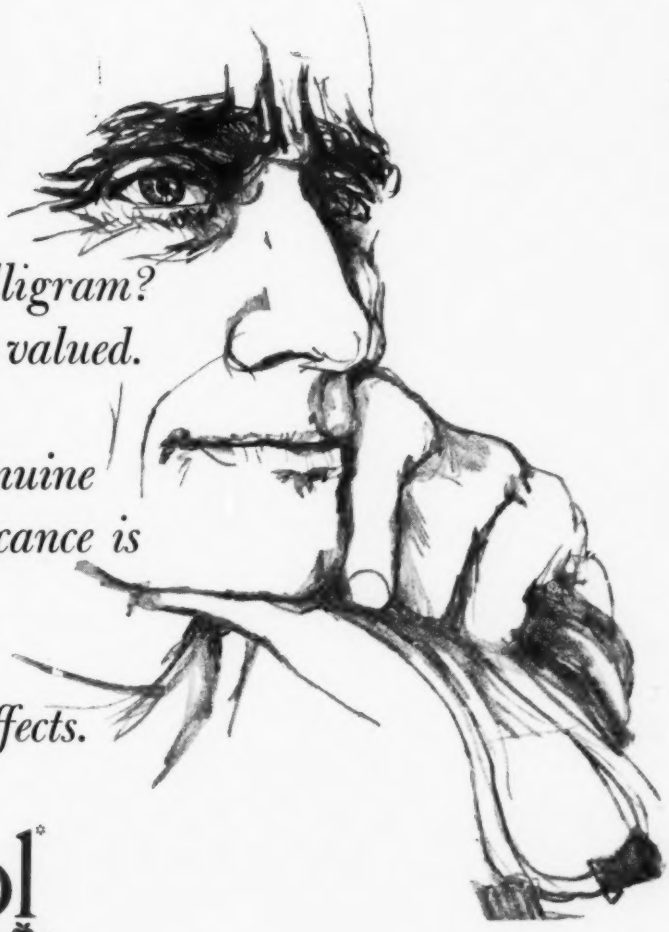

CRITERIA

Tablet size?
Potency per milligram?
Often these are valued.
But the only
criterion of genuine
clinical significance is
the ratio of
desired effects
to undesired effects.
Hence . . .

Medrol*

the corticosteroid that hits the disease, but spares the patient

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"'JUST A LITTLE CASE OF CYSTITIS'...

"'Just a little case of cystitis' may actually have already involved the kidney parenchyma before the bladder became infected."[1]

"The first evidence of inflammatory disease of kidney or prostate often is vesical irritability."[2]

WHEN THE SYMPTOMS IS CYSTITIS

FURADANTIN®

brand of nitrofurantoin

for rapid control of infection throughout the G. U. system

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, Proteus and certain strains of Pseudomonas, resistant to other agents ■ actively excreted by the tubule cells in addition to glomerular filtration ■ negligible development of bacterial resistance after 7 years of extensive clinical use ■ excellent tolerance—nontoxic to kidneys, liver and blood-forming organs ■ safe for long-term administration

AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. q.i.d. with meals and with food or milk on retiring. Supplied: Tablets, 50 and 100 mg., Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Editorial: J.M.A. Georgia **46**:433, 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953, p. 330.

NITROFURANS—a unique class of antimicrobials—neither antibiotics nor sulfonamides

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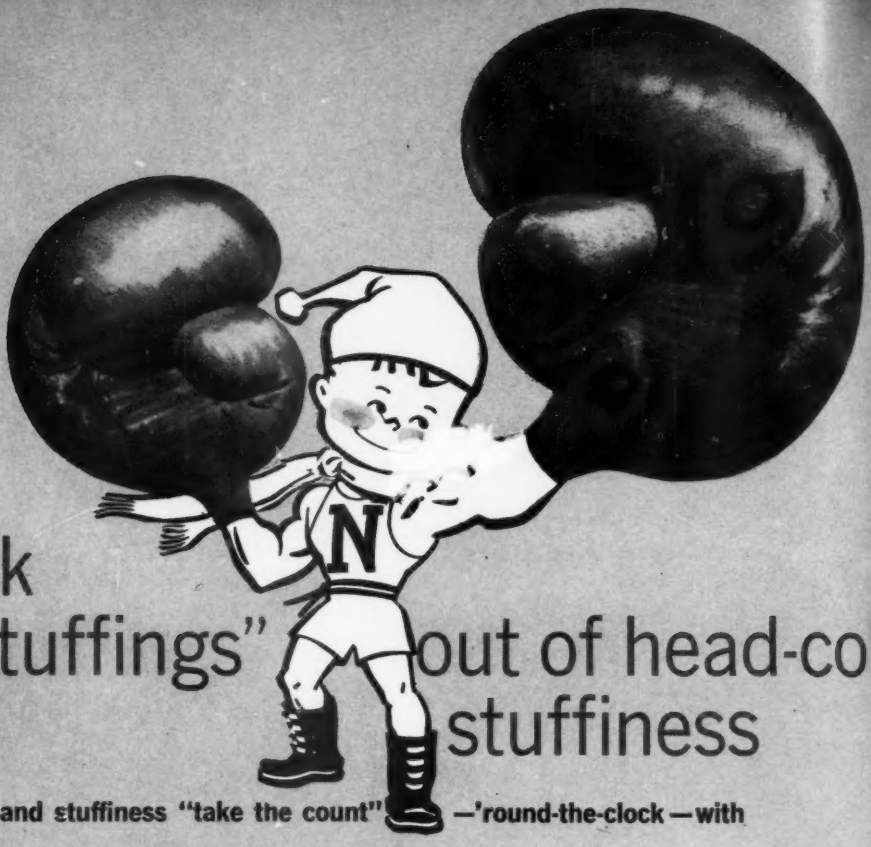

"Knock the stuffings" out of head-cold stuffiness

Sniffles and stuffiness "take the count" —'round-the-clock—with

Naldecon™

The long-acting nasal decongestant with the therapeutic "one-two" tablets

Awake or asleep, your "cold patient" can be kept comfortably free of nasal dripping and congestion, watery eyes and stuffy head. These distressing symptoms are gently but effectively "knocked out" by long-acting Naldecon's therapeutic one-two:

"One"—a combination of 2 potent decongestants, to reduce mucosal swelling.

"Two"—a combination of 2 dependable antihistaminics, to relieve allergic symptoms.

Relief — within minutes — is easily maintained 'round-the-clock, with t.i.d. dosage of this unique nasal decongestant.

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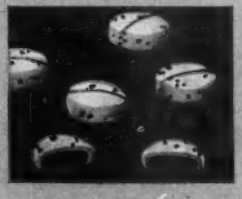
SYRACUSE, NEW YORK



NALDECON TABLETS

Each long-acting NALDECON "tablet-within-a-tablet" contains:

	Outer Layer (3 to 4 hours relief)	Inner Core (additional 3 to 4 hours relief)	Total Content (5 to 8 hours relief)
DECONGESTANTS:			
Phenylephrine HCl	5 mg.	5 mg.	10 mg.
Phenylpropanolamine HCl	20 mg.	20 mg.	40 mg.
ANTIHISTAMINICS:			
Phenyltoloxamine citrate	7.5 mg.	7.5 mg.	15 mg.
Chlorpheniramine maleate	2.5 mg.	2.5 mg.	5 mg.

Dosage, Naldecon Tablets — Adults and children over 12: One tablet morning, afternoon and evening for 'round-the-clock relief. Children [illegible] 12: One-half tablet morning, afternoon and evening.

Also available — NALDECON SYRUP

Each teaspoonful (5 cc.) of NALDECON Syrup contains: phenylephrine HCl, 5 mg.; phenylpropanolamine HCl, 20 mg.; phenyltoloxamine citrate, 7.5 mg., and chlorpheniramine maleate, 2.5 mg.

Dosage, Naldecon Syrup—Adults and children over 12: One tsp. (5 cc.) every 3 or 4 hours. Children 6 to 12: One-half tsp. every 3 or 4 hours. Under 6: In proportion.

Just one prescription for Engran "Term-Pak" (270 TABLETS)
SQUIBB VITAMIN-MINERAL SUPPLEMENT
calling for one tablet a day will carry her through term to the six-week postpartum checkup. This means you are assured of a nutritionally perfect pregnancy, and she realizes major savings.*

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'ENGRAN'®, 'TERM-PAK' AND 'FLEXIDOSE' ARE SQUIBB TRADEMARKS

* *And when baby comes, specify* Engran baby drops—*full* vitamin support in *half the volume* of most similar preparations — lasts twice as long. Supplied in 15 cc. and 50 cc. bottles. Convenient 'Flexidose' Dropper assures accurate dosage.

when the
rheumatic
disorder
is more
than salicylates
alone
can control...

MORE
HIGHLY INDIVIDUALIZED
THERAPY
FOR THE
RHEUMATIC
"IN-BETWEEN"

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Aristo

wider latitude in adjusting dosage

ARISTOGESIC is particularly effective for relief of chronic – but less severe – pain of rheumatic origin. ARISTOGESIC combines the anti-inflammatory effects of ARISTOCORT® Triamcinolone with the analgesic action of salicylamide, a highly potent salicylate. Dosage requirements for ARISTOGESIC are substantially lower than generally required for each agent alone. The exceptionally wide latitude of dosage adjustment with ARISTOGESIC permits well-tolerated therapy for long periods of time with fewer side effects.

Indications: Mild cases of rheumatoid arthritis, tenosynovitis, synovitis, bursitis, mild spondylitis, myositis, fibrositis, neuritis, and certain muscular strains.

Dosage: Average initial dosage: 2 capsules 3 or 4 times daily. Maintenance dosage to be adjusted according to response.

Precautions: All precautions and contraindications traditional to corticosteroid therapy should be observed. The amount of drug used should be carefully adjusted to the lowest dosage which will suppress symptoms. Discontinuance of therapy must be carried out gradually after patients have been on steroids for prolonged periods.

Each ARISTOGESIC Capsule contains:

ARISTOCORT® Triamcinolone	0.5 mg.
Salicylamide	325 mg.
Dried Aluminum Hydroxide Gel	75 mg.
Ascorbic Acid	20 mg.

Supply: Bottles of 100 and 1,000.

gesic® Capsules

Steroid-Analgesic Compound LEDERLE

Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

greater antihypertensive effect...fewer side effects

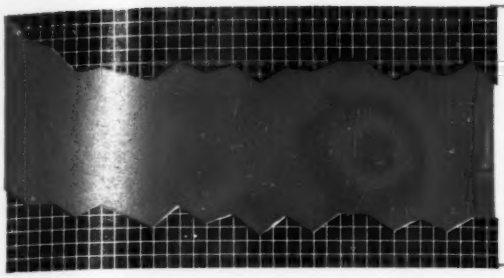
HYDROPRES

HYDRODIURIL® HYDROCHLOROTHIAZIDE antihypertensive

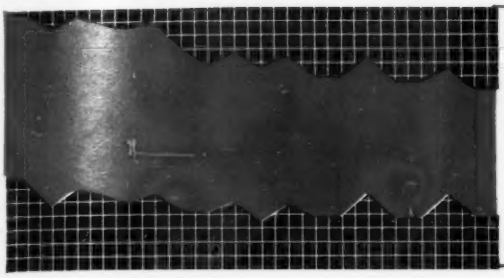
WITH

RESERPINE antihypertensive-tranquilizer

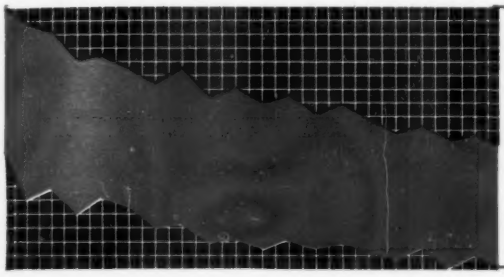
For complete information write Professional Services, Dept. H6, Merck Sharp & Dohme, West Point, Pa.



HYDRODIURIL alone



RESERPINE alone



HYDROPRES
much more effective than either of its components alone

- Effective by itself in a majority of patients. Provides smooth, more trouble-free management of hypertension.
- Since HYDRODIURIL and reserpine potentiate each other, the required dosage of each is lower when given together as HYDROPRES than when either is given alone.
- HYDROPRES provides the needed and valuable tranquilizing effect of reserpine. Lower dosage may reduce such side effects of reserpine as excessive sedation and depression.
- Arrest or reversal of organic changes of hypertension may occur.
- Headache, dizziness, palpitations and tachycardia are usually promptly relieved. Anginal pain may be reduced in incidence and severity.
- With HYDROPRES, dietary salt may be liberalized.
- Convenient, controlled dosage.

HYDROPRES-25
25 mg. HYDRODIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

HYDROPRES-50
50 mg. HYDRODIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

MSD **MERCK SHARP & DOHME,** DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

®HYDRODIURIL AND HYDROPRES ARE TRADEMARKS OF MERCK & CO., INC.

new hope for fetal salvage

DELA

The results of administering Delalutin before the 12th week of gestation to 82 women with habitual abortion were reported recently by Reifenstein[1] in a compilation of data supplied by 45 investigators. Every patient had experienced at least three consecutive abortions immediately preceding the treated pregnancy. More than 68% of these women were delivered successfully and uneventfully following Delalutin therapy.

Boschann,[2] in a study of pregnancies with threatened abortion, found that:

37% of 73 pregnancies were carried to term without progestational therapy

64% of 42 pregnancies were salvaged by progesterone

83% of 73 pregnancies were salvaged by Delalutin

Eichner,[3] found that in Delalutin-treated women, fetal salvage of infants below term weight (1000 to 2000 gm.) was significantly improved. 108 (76%) of 142 babies of this birth weight survived without mothers receiving progestational therapy, while 16 (100%) of 16 babies of this birth weight survived with mothers receiving Delalutin therapy. A comparison study was made of a group of repeated aborters treated with Delalutin, and a group with a similar history treated with bed rest and sedation.[4] Pregnancy salvage with Delalutin was twice that of the control group. Delalutin was found to be "highly active", well-tolerated and long-acting.

According to Tyler and Olson,[5] "These qualities of prolonged action and relative freedom from local reactions make [Delalutin] a generally more desirable therapeutic agent for intramuscular use than progesterone . . . ."

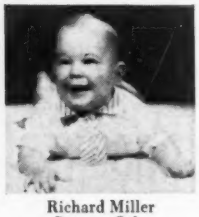
DELALUTIN BABIES WHOSE MOTHERS WERE HABITUAL ABORTE

Mary Ann Cribben
Garden City, N. Y.

Amy Sue Greenman
Lincolnwood, Ill.

William Peller
Skokie, Ill.

Randy Sinis
Denver, Colo.



Richard Miller
Denver, Colo.

Scott Knudsen
Norwich, Vt.

References: 1. Reifenstein, E. C. Jr.: *Annals N. Y. Acad. Sc.* 71:762 (July 30) 1958. 2. Boschann, H.W.: *ibid.*, p. 727. 3. Eichner, E.: *ibid.*, p. 787. 4. Hodgkinson, C. P.; Igna, E. J., and Bukeavich, A. P.: *Am. J. Obst. & Gynec.* 76:279, 1958. 5. Tyler, E. T., and Olson, H. J.: *J.A.M.A.* 169:1843, 1959.

LUTIN

improved progestational therapy

SQUIBB HYDROXYPROGESTERONE CAPROATE

***DELALUTIN** offers these advantages over other progestational agents:*

- long-acting sustained therapy
- more effective in producing and maintaining a completely matured secretory endometrium
- no androgenic effect
- more concentrated solution requiring injection of less vehicle
- unusually well-tolerated, even in large doses
- fewer injections required
- low viscosity makes administration easier

DELALUTIN is also potent and safe therapy for: threatened abortion; postpartum afterpains; amenorrhea, primary and secondary; dysfunctional uterine bleeding not associated with genital malignancy; infertility with inadequate corpus luteum function; production of secretory endometrium and desquamation during estrogen therapy; premenstrual tension; dysmenorrhea; cyclomastopathy, mastodynia, adenosis and chronic cystic mastitis.

Administration and dosage:

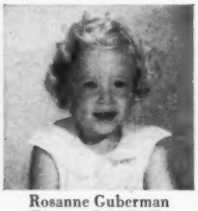
Because of its low viscosity, Delalutin may be administered with a small gauge needle (deep intragluteal injection). Complete information on administration and dosage is supplied in the package insert.

Supply:

Delalutin is available in vials of 2 and 10 cc., each containing 125 mg. of hydroxyprogesterone caproate in sesame oil, and benzyl benzoate.

Each of these healthy, normal babies was born by a mother with a documented previous history of true habitual abortion, who was treated during her most recent pregnancy with DELALUTIN.

Nina Rutkowski
Roselle, Ill.



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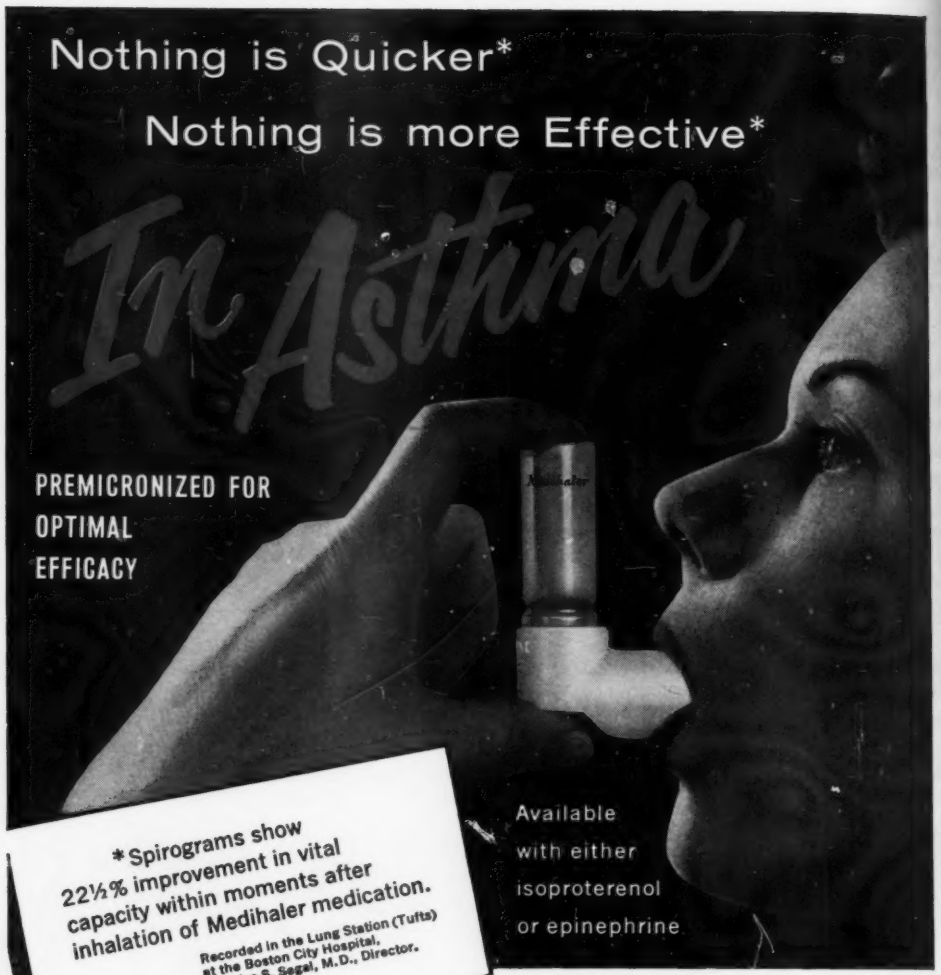
SQUIBB *Squibb Quality—the Priceless Ingredient*

"DELALUTIN" IS A SQUIBB TRADEMARK.

Nothing is Quicker*

Nothing is more Effective*

In Asthma



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*Spirograms show 22½% improvement in vital capacity within moments after inhalation of Medihaler medication.

Recorded in the Lung Station (Tufts) at the Boston City Hospital, Maurice S. Segal, M.D., Director.

Available with either isoproterenol or epinephrine

Automatically measured-dose aerosol medications.
Nonbreakable...Shatterproof
Spillproof...Leakproof

Medihaler-ISO® Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.06 mg. isoproterenol.

Medihaler-EPI® Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose contains 0.15 mg. epinephrine.

NOTABLY WELL TOLERATED AND EFFECTIVE FOR CHILDREN, TOO

Riker Northridge, Calif.

Donnagel®

Robins

or Donnagel® with Neomycin

Prompt and more dependable control of virtually all diarrheas can be achieved with the comprehensive DONNAGEL formula, which provides adsorbent, demulcent, antispasmodic and sedative effects—with or without an antibiotic. Early re-establishment of normal bowel function is assured—for all ages, in all seasons.

DONNAGEL: In each 30 cc. (1 fl. oz.):

Kaolin (90 gr.)	6.0 Gm.
Pectin (2 gr.)	142.8 mg.
Hyoscyamine sulfate	0.1037 mg.
Atropine sulfate	0.0194 mg.
Hyoscine hydrobromide	0.0065 mg.
Phenobarbital (¼ gr.)	16.2 mg.

DONNAGEL WITH NEOMYCIN

Same formula, plus

Neomycin sulfate	300 mg.

(Equal to neomycin base, 210 mg.)

A. H. ROBINS CO., INC., Richmond 20, Virginia · *Ethical Pharmaceuticals of Merit since 1878*

because many diseases involve emotional and physical stress...

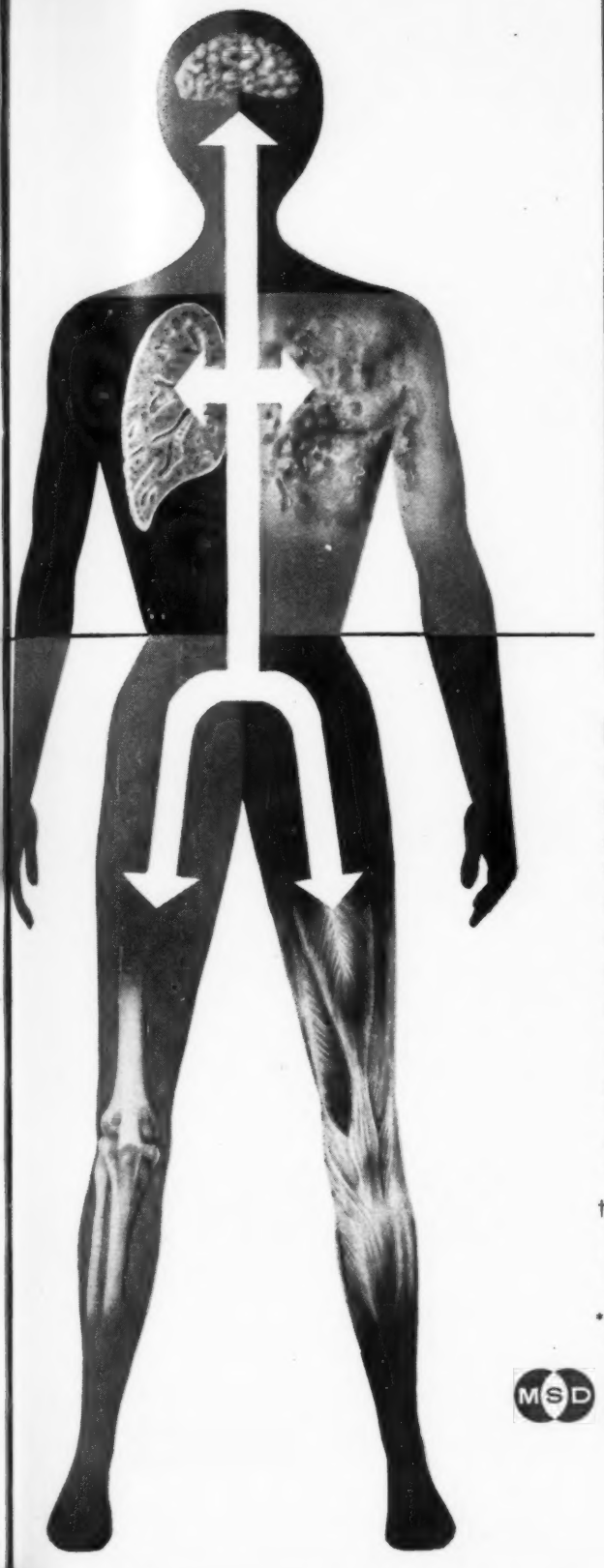
in arthritic and rheumatic disorders†

NEW

DECABAMATE*

DECADRON® dexamethasone with Meprobamate

treats more of the patient more effectively



DECABAMATE links the action of DECADRON®, the most potent and effective of the anti-inflammatory steroids, with the most widely accepted and well tolerated of the muscle-relaxant tranquilizers, meprobamate . . .
By treating more of the patient more effectively, DECABAMATE can make the difference between disability and employability in many rheumatic and arthritic conditions.

Dosage Range: One or two tablets t.i.d. or q.i.d.

Supplied: As scored yellow tablets providing 0.25 mg. DECADRON plus 200 mg. meprobamate; bottles of 100.

Additional information on DECABAMATE is available to the physician on request.

† Rheumatoid arthritis, including palindromic rheumatism, rheumatoid spondylitis, Still's disease, and psoriatic arthritis. Acute, painful inflammatory musculoskeletal conditions (i.e., bursitis, synovitis, and tenosynovitis).

* DECABAMATE and DECADRON are trademarks of Merck & Co., Inc.

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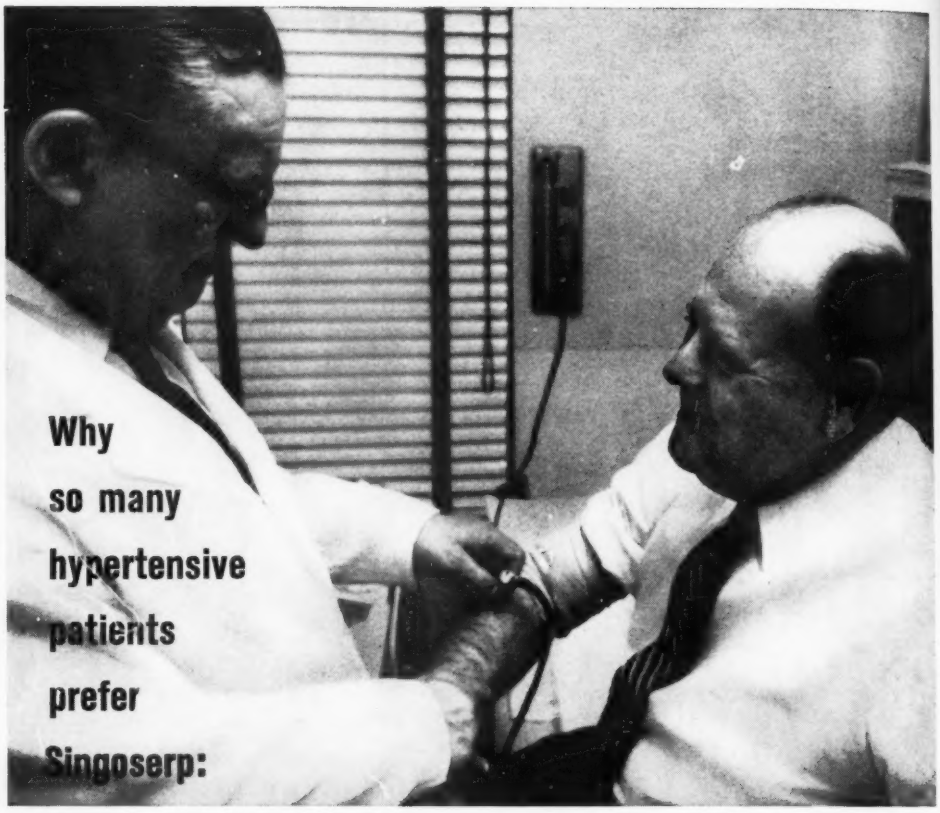

It spares them from the usual rauwolfia side effects

FOR EXAMPLE: "A clinical study made of syrosingopine [Singoserp] therapy in 77 ambulant patients with essential hypertension demonstrated this agent to be effective in reducing hypertension, although the daily dosage required is higher than that of reserpine. Severe side-effects are infrequent, and this attribute of syrosingopine is its chief advantage over other Rauwolfia preparations. The drug appears useful in the management of patients with essential hypertension."*

*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. **169**:1609 (April 4) 1959.

Remember SERPASIL® (reserpine CIBA) for the anxious hypertensive with or without tachycardia

Singoserp®

(syrosingopine CIBA)

First drug to try in new hypertensive patients

First drug to add in hypertensive patients already on medication

SUPPLIED: Singoserp *Tablets*, 1 mg. (white, scored); bottles of 100. Samples available on request. Write to CIBA, Box 277, Summit, N. J.

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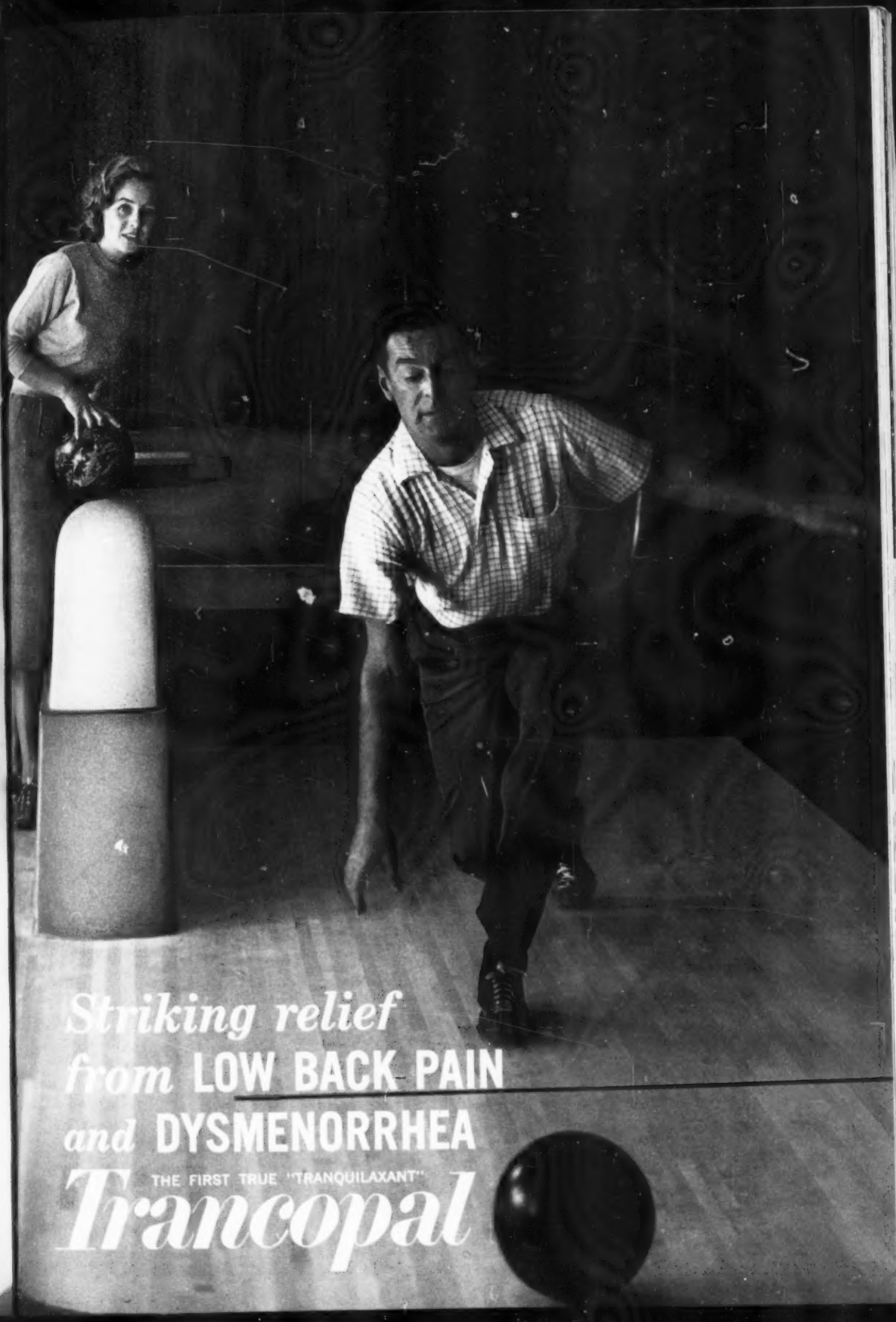

Striking relief
from LOW BACK PAIN
and DYSMENORRHEA
THE FIRST TRUE "TRANQUILAXANT"
Trancopal

Here is what you can expect when you prescribe

for dysmenorrhea
and premenstrual tension

Case Profile*

A 28-year-old married woman, a secretary in a booking agency, complained of severe and consistent pain and cramps in the abdomen during her menstrual periods. Psychologically, she described the first two days as "climbing the walls." Menarche occurred at age 13. She has a regular twenty-eight day menstrual cycle and a four day menstrual period.

Trancopal was given in a dose of 100 mg. four times a day for the first two days of the four day period. In addition to the relief of the dysmenorrhea she also noticed disappearance of a "bloated feeling" that had previously annoyed her. She has now been treated with Trancopal for one and one-half years with excellent results. Other medication, such as codeine or aspirin with codeine, had relieved the pain, but the patient had had to stay home. Because her father is a physician, many commercial preparations had been tried prior to Trancopal, but no success had been achieved.

Before taking Trancopal this patient missed one day of work every month. For the past year and a half she has not missed a day because of dysmenorrhea.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

for low back pain

Case Profile*

A 42-year-old truck driver and mover injured his back while moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck. The muscle spasm was completely controlled and no apparent side effects were noted.

For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal

potent MUSCLE RELAXANT

effective TRANQUILIZER

- In musculoskeletal disorders, effective in 91 per cent of patients.[1]
- In anxiety and tension states, effective in 89 per cent of patients.[1]
- Low incidence of side effects (2.3 per cent of patients). Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. It does not affect the hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications [1-6]

Musculoskeletal:

Low back pain (lumbago, etc.)
Neck pain (torticollis)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disc syndrome
Fibrositis
Ankle sprain, tennis elbow
Myositis
Postoperative muscle spasm

Psychogenic:

Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris
Alcoholism

Now available in two strengths:

Trancopal Caplets®,
100 mg. (peach colored, scored), bottles of 100.

NEW STRENGTH ▶

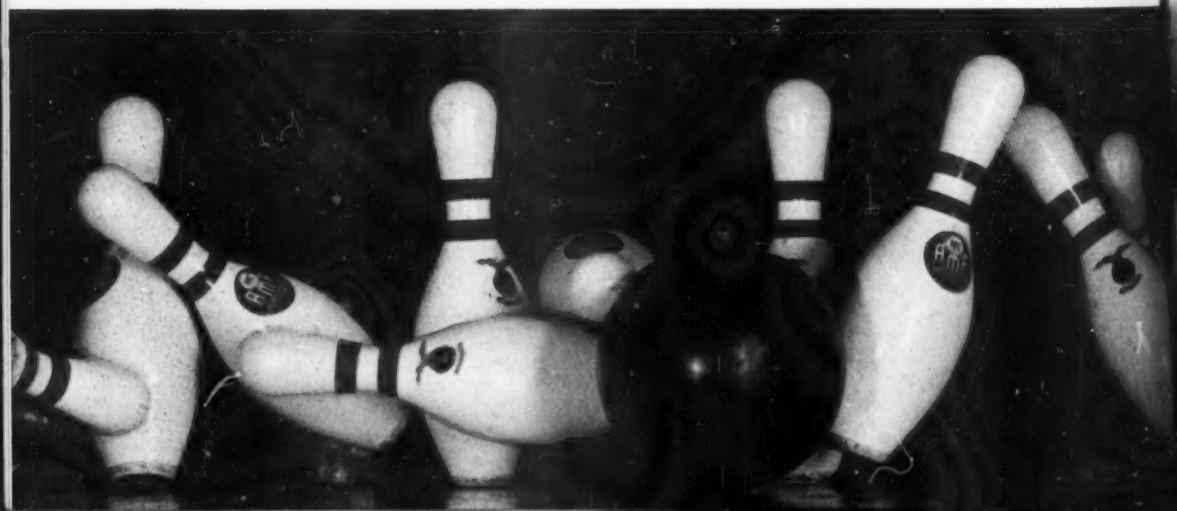
Trancopal Caplets,
200 mg. (green colored, scored), bottles of 100.

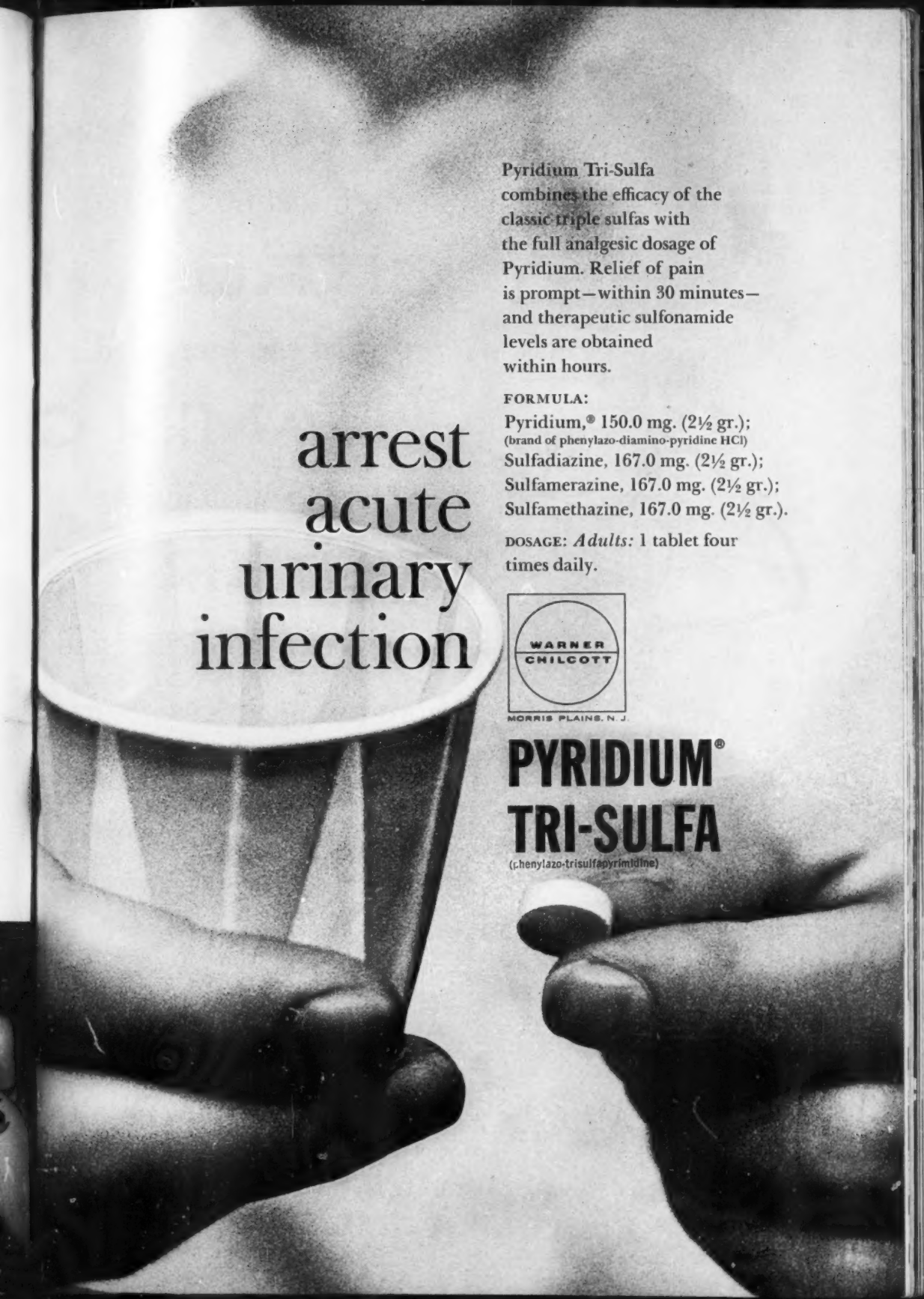
Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Winthrop LABORATORIES
New York 18, N. Y.

References: 1. Collective Study, Department of Medical Research, Winthrop Laboratories. 2. Lichtman, A. L.: New developments in muscle relaxant therapy, *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 3. Lichtman, A. L.: Relief of muscle spasm with a new central muscle relaxant, chlormezanone (Trancopal), Scientific Exhibit, Meeting of the International College of Surgeons, Miami Beach, Fla., Jan. 4-7, 1959. 4. Ganz, S. E.: Clinical evaluation of a new muscle relaxant (chlormethazanone), *J. Indiana M. A.* 52:1134, July, 1959. 5. Mullin, W. G., and Epifano, Leonard: Chlormezanone, a tranquilizing agent with potent skeletal muscle relaxant properties, *Am. Pract. Digest Treat.* 10:1743, Oct., 1959. 6. Shanaphy, J. F.: Chlormezanone (Trancopal) in the treatment of dysmenorrhea; a preliminary report, *Current Therap. Res.* 1:59, Oct., 1959.

Trancopal (brand of chlormezanone) and Caplets, trademarks reg. U.S. Pat. Off. 1408M Printed in U.S.A.




arrest
acute
urinary
infection
Pyridium Tri-Sulfa
combines the efficacy of the
classic triple sulfas with
the full analgesic dosage of
Pyridium. Relief of pain
is prompt—within 30 minutes—
and therapeutic sulfonamide
levels are obtained
within hours.
FORMULA:
Pyridium,® 150.0 mg. (2½ gr.);
(brand of phenylazo-diamino-pyridine HCl)
Sulfadiazine, 167.0 mg. (2½ gr.);
Sulfamerazine, 167.0 mg. (2½ gr.);
Sulfamethazine, 167.0 mg. (2½ gr.).
DOSAGE: Adults: 1 tablet four
times daily.
WARNER
CHILCOTT
MORRIS PLAINS, N. J.
PYRIDIUM®
TRI-SULFA
(phenylazo-trisulfapyrimidine)

in the season of

acute infections, extra

CITRUS

provides the increased

VITAMIN C

and fluid needed during

FEVER

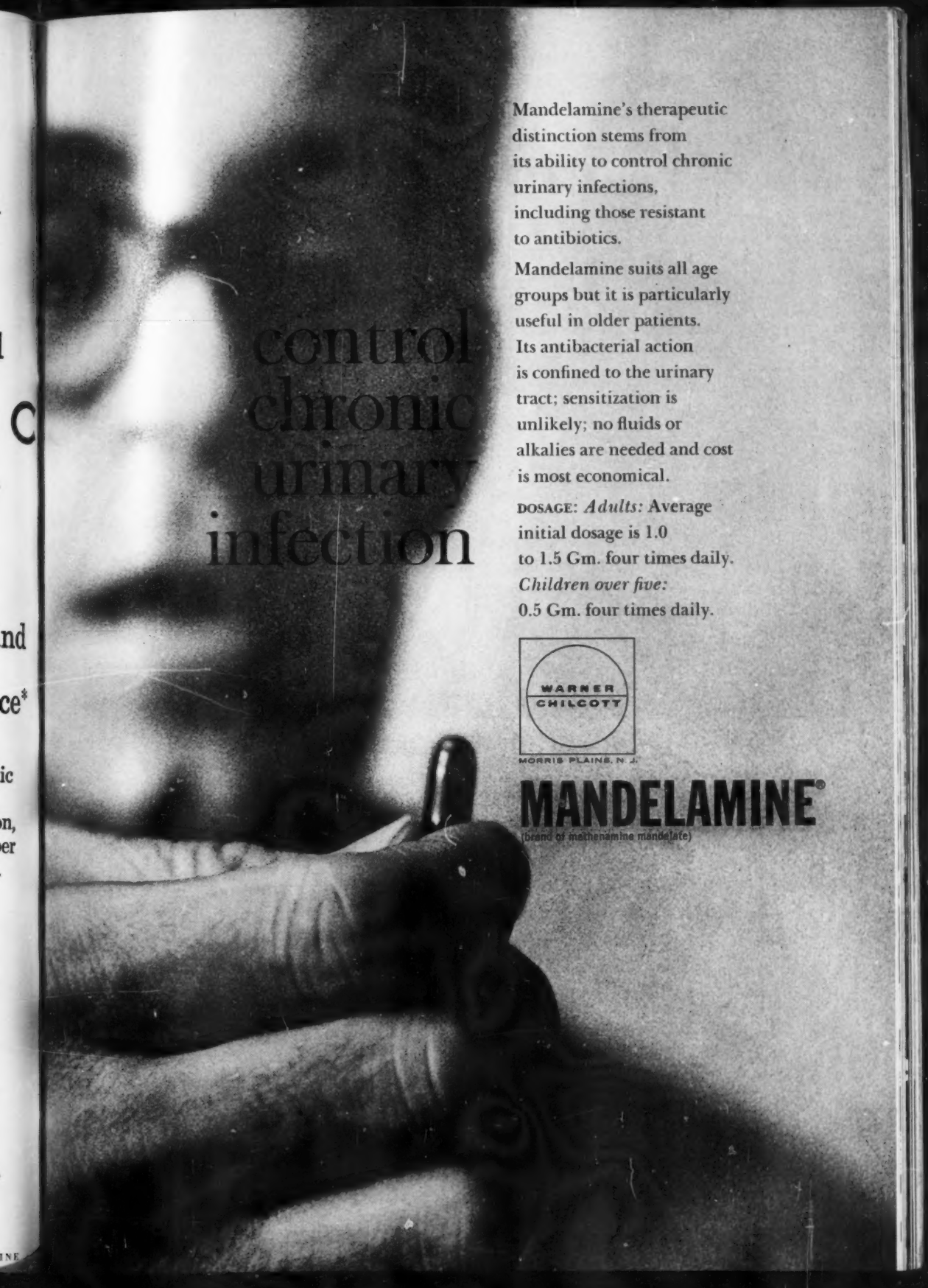
to prevent deficiency and

help maintain resistance*

*Tisdall and Jolliffe note the systemic relation in animals between vitamin C and resistance to infection, with increased needs evident in upper respiratory streptococcal infections.

– In: Clinical Nutrition ed. by Norman Jolliffe et al. New York, Paul B. Hoeber, Inc., 1950, pp. 590-91, 637-38.

FLORIDA CITRUS COMMISSION • LAKELAND, FLORIDA



Mandelamine's therapeutic distinction stems from its ability to control chronic urinary infections, including those resistant to antibiotics.

Mandelamine suits all age groups but it is particularly useful in older patients. Its antibacterial action is confined to the urinary tract; sensitization is unlikely; no fluids or alkalies are needed and cost is most economical.

DOSAGE: *Adults:* Average initial dosage is 1.0 to 1.5 Gm. four times daily. *Children over five:* 0.5 Gm. four times daily.

WARNER CHILCOTT

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MANDELAMINE®

(brand of methenamine mandelate)

PROVEN EFFECTIVE FOR THE TENSE AND NERVOUS PATIENT

"There is perhaps no other drug introduced in recent years which has had such a broad spectrum of clinical application as has meprobamate.* As a tranquilizer, without an autonomic component in its action, and with a minimum of side effects, meprobamate has met a clinical need in anxiety states and many organic diseases with a tension component."

Krantz, J. C., Jr.: The restless patient – A psychologic and pharmacologic viewpoint. Current M. Digest *25*:68, Feb. 1958.

*Miltown®

the original meprobamate, discovered and introduced by
WALLACE LABORATORIES, *New Brunswick, N. J.*

CM-212

you need the protection of **TRUE SECURITY**

Few men need to buy four thousand dollars worth of equipment just to get started, as you probably did. That extra expense is only one of the many unusual financial hurdles in a medical career. Even with an above average income, it takes wise planning to meet these special problems and at the same time provide for your family's protection.

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The more potent

the greater the need for

Physiologic Balance[1]

start...alternate...terminate

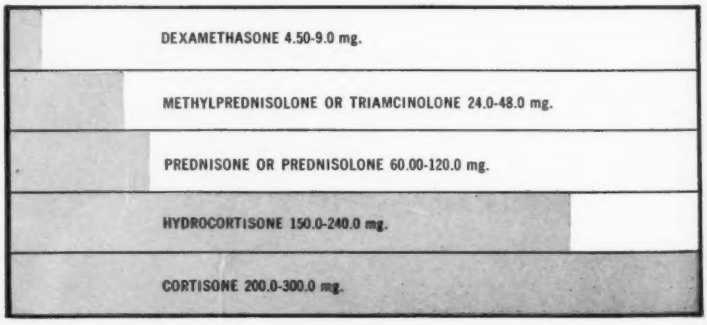
with potent, long-acting, intramuscular

Cortrophin®

the specific, physiologic adrenocortical stimulant

Balance corticosteroid therapy with Cortrophin-Zinc

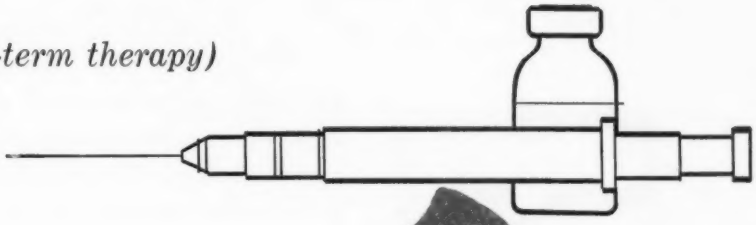
After every 6 days' SYSTEMIC THERAPY WITH:



On the 7th day OMIT THE CORTICOSTEROID AND INJECT CORTROPHIN-ZINC, 40 U.S.P. UNITS, I.M.

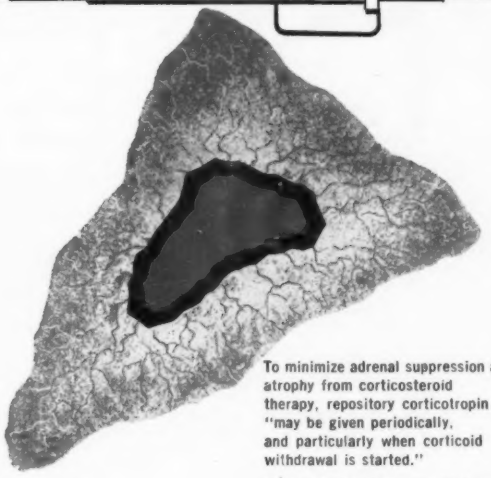
the systemic corticosteroid...

(even in short-term therapy)



-Zinc

corticotropin-alpha zinc hydroxide (ORGANON)



To minimize adrenal suppression and atrophy from corticosteroid therapy, repository corticotropin "may be given periodically, and particularly when corticoid withdrawal is started."

(Report to A.M.A. Council on Drugs: J.A.M.A. **169**:1063, 1959)

- **Stimulate the adrenal cortex**
- **Maintain resistance to stress**
- **Avoid post-therapy adrenal insufficiency**

CORTROPHIN-ZINC: 40 or 20 U.S.P. units/cc., 5-cc. vials, 1-cc. sterile, disposable syringes. "Produces a more prolonged hormone effect . . . more potent and longer acting than gel ACTH . . . a free flowing substance that can be injected in a very small gauge needle."[2]

1. Krusius, F. E., and Oka, M.: Ann. Rheumat. Dis. *17*:184, 1958.
2. Siegel, S. C.: Lederle Symposium Report, *1*:43, 1958.

Organon

Organon Inc., Orange, New Jersey

FOR GREATER LATITUDE IN SOLVING THE PROBLEM **HYPERTENSION** WITHOUT SIGNIFICANT POTASSIUM DEPLETION

RAUTRAX, a combination of Raudixin with Ademol (flumethiazide)—**the new, safe nonmercurial diuretic**—controls all degrees of hypertension. Elimination of excess extracellular sodium and water is rapid and safe.[1-5] Potassium loss is less than with other nonmercurial diuretics;[1-3] and, in addition, Rautrax increases protection against potassium and chloride depletion during long-term management by including supplemental potassium chloride.

The dependable diuretic action of Ademol rapidly controls the clinical and subclinical edema often associated with cardiovascular disease. And after Rautrax has normalized the fluid balance, the normal serum electrolyte pattern is not altered appreciably by continued administration.[4] Ademol also potentiates the antihypertensive action of Raudixin.[1] In this way a lower dose of each component controls hypertension effectively and safely . . . with fewer side effects.

REFERENCES: 1. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: New England J. Med. 260:872 (April 23) 1959. 2. Fuchs, M.; Bodi, T., and Moyer, J. H.: Am. J. Cardiol. 3:676 (May) 1959. 3. Fuchs, M., and others: Monographs on Therapy 4:43 (April) 1959. 4. Montero, A. C.; Rochelle, J. B., III, and Ford, R. V.: Am. Heart J. 57:484 (April) 1959. 5. Rochelle, J. B., III; Montero, A. C., and Ford, R. V.: Antibiotic Med. & Clin. Ther. 6:267 (May) 1959. LITERATURE AVAILABLE ON REQUEST

SQUIBB

Squibb Quality—
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NEW RAUTRAX

RAUDIXIN (Squibb standardized whole root Rauwolfia Serpentina) / ADEMOL (Squibb Flumethiazide) / POTASSIUM CHLORIDE

'RAUDIXIN' ®, 'RAUTRAX' AND 'ADEMOL' ARE SQUIBB TRADEMARKS

he's
comfortable
now

No more
coughing.
His physician prescribed
pleasant-tasting,
cream-mint
Syrup PHENERGAN FORTIS.

He's relaxed,
less irritable, more cheerful.
No more coughing,
nausea or vomiting.

He'll sleep well too
(and so will his parents).

for symptomatic relief of
coughing, emesis, and restlessness

SYRUP 25 mg./5 cc.
PHENERGAN® FORTIS
HYDROCHLORIDE
Promethazine Hydrochloride, Wyeth

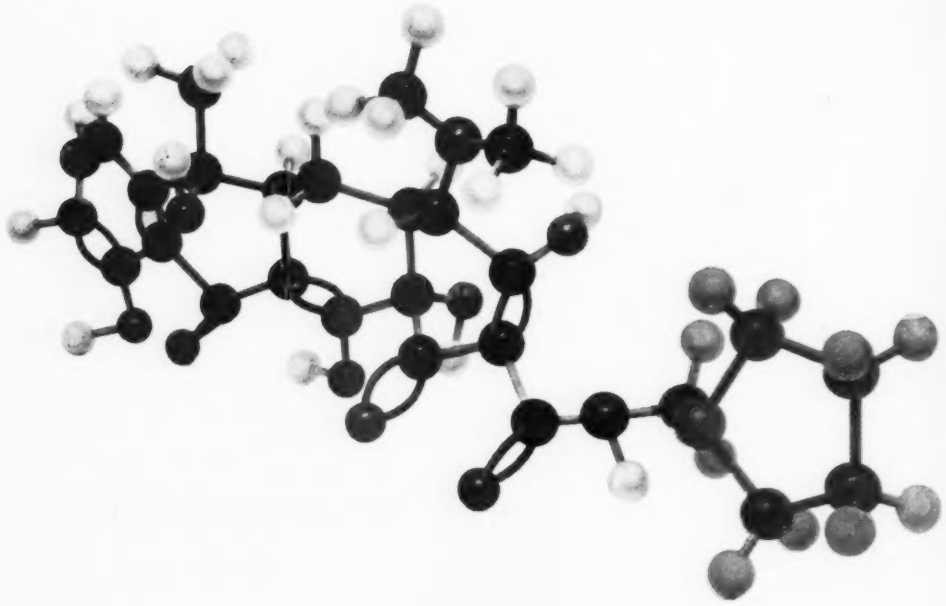
Wyeth®
Philadelphia 1, Pa.

NOW AVAILABLE FROM BRISTOL LABORATORIES

SYNTETRIN™

N–(PYRROLIDINOMETHYL) TETRACYCLINE

a new[1] improved broad-spectrum antibiotic for parenteral administration



SYNTETRIN – a new synthetic derivative of tetracycline – has these attributes of significant value in therapy:

- effective antibacterial activity is sustained – *even at its lowest blood levels* – throughout therapy
- total antibiotic activity of SYNTETRIN I.M. more than twice that with tetracycline phosphate complex I.M. over a 24-hour period
- highly soluble over the entire physiological pH range (2,500 times more soluble than tetracycline) resulting in more efficient absorption from intramuscular sites than other tetracycline I.M. preparations

An important advantage of SYNTETRIN is that the *lowest* blood levels reached before ensuing daily injections are either maintained or increased. This means that antibiotic levels will not drop below those required to inhibit certain pathogens during the course of therapy. Successive blood level peaks generally rise after repeated injections.

***Parenteral* SYNTETRIN** is recommended for initial therapy in infections caused by tetracycline-sensitive organisms in:

1. Patients who require frequent force-feeding or special diets based on milk, which interfere with antibiotic absorption.
2. Patients with diseases causing absorption difficulties.
3. Patients unable to take anything by mouth.

1. Gottstein, W. J.; Minor, W. F., and Cheney, L. C.: J. Am. Chem. Soc. 81:1198, 1959.

for intramuscular injection

SYNTETRIN I.M.

N–(PYRROLIDINOMETHYL) TETRACYCLINE WITH XYLOCAINE®* FOR INTRAMUSCULAR USE

Supplied in dry-fill single dose vials:

SYNTETRIN I.M. '350' contains:		SYNTETRIN I.M. '150' contains:	
SYNTETRIN	350 mg.	SYNTETRIN	150 mg.
Lidocaine	40 mg.	Lidocaine	40 mg.
Ascorbic Acid	300 mg.	Ascorbic Acid	300 mg

*Xylocaine is the registered trademark of Astra Pharmaceutical Products, Inc. for lidocaine.

for intravenous infusion

SYNTETRIN I.V.

N–(PYRROLIDINOMETHYL) TETRACYCLINE FOR INTRAVENOUS INFUSION

Supplied in dry-fill vials, each containing: SYNTETRIN ..... 700 mg.
Ascorbic Acid ..... 500 mg.

Detailed information on indications, dosage and precautions is contained in package insert; or, write to Medical Director, Bristol Laboratories Inc., New York, New York.

BRISTOL

while they are planning
their family

**they need your help
more than ever**

the most widely prescribed contraceptive

WHENEVER A DIAPHRAGM IS INDICATED

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when holiday dinners include food allergens

BENADRYL®

ANTIHISTAMINIC-ANTISPASMODIC

gives prompt, comprehensive relief

The patient allergic to certain foods may find holiday menus a temptation difficult to resist. When he yields to allergenic dishes, BENADRYL brings him prompt relief from gastrointestinal distress. BENADRYL also helps to control cutaneous reactions and respiratory symptoms so often associated with food sensitivity. BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a variety of forms, including Kapseals,® 50 mg. each; Kapseals, 50 mg., with ephedrine sulfate, 25 mg.; Capsules, 25 mg. each; Elixir, 10 mg. per 4 cc.; and for delayed action, Emplets,® 50 mg. each. For parenteral therapy, BENADRYL Hydrochloride Steri-Vials,® 10 mg. per cc.; and Ampoules, 50 mg. per cc.

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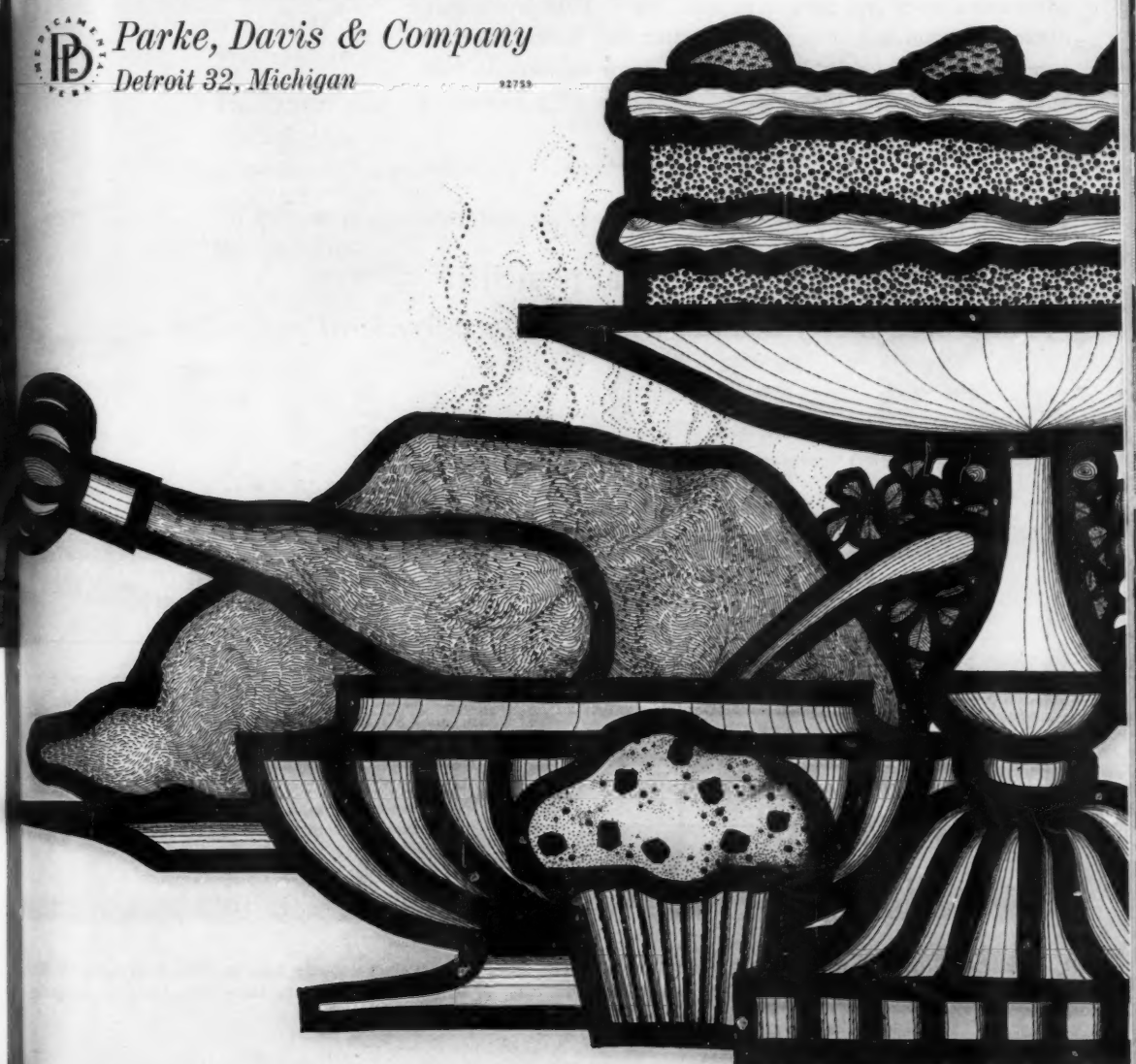
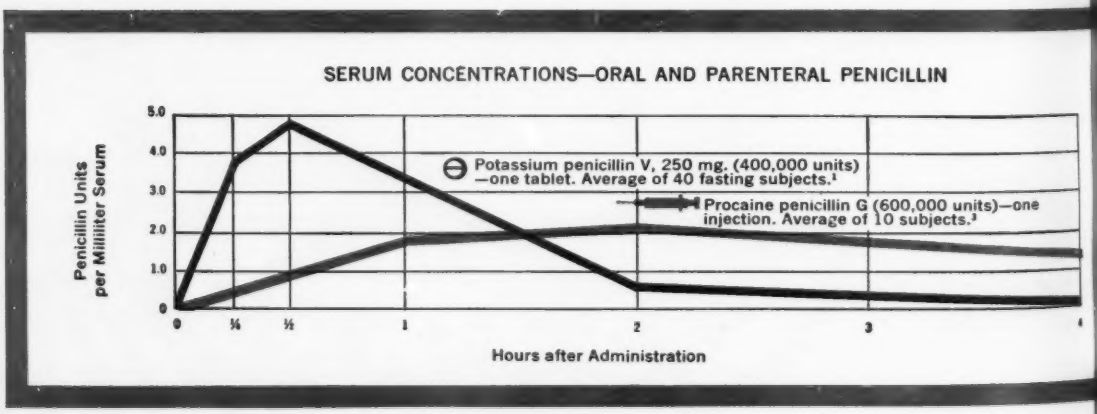


in oral penicillin therapy

the speed of action you want the reliability you need

In recent studies involving 107 subjects, effective penicillin blood levels were *consistently* produced within 15 minutes after administration of oral potassium penicillin V. Peak levels were obtained within a half-hour. Even after two hours, effective penicillin blood levels still persisted in *every* subject. At four hours, demonstrable blood levels existed in 93 per cent of subjects.[1-2]

PEN·VEE K may be prescribed for
all infections responsive to oral penicillin
. . . and even many usually treated with parenteral penicillin



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The antibiotic that is prescribed most often for common bacterial infections . . .

penicillin

In a form that produces high penicillin blood levels rapidly and reliably . . .

potassium penicillin V

In two dosage strengths and preparations to assure acceptance by patients . . .

PEN·VEE® K

Liquid: Penicillin V Potassium for Oral Solution; Tablets: Penicillin V Potassium, Wyeth

LIQUID

flexibility of dosage form and high potency assure acceptability of full therapeutic dosage

SUPPLIED: *Liquid*: raspberry-flavored, 125 mg. (200,000 units) per 5-cc. teaspoonful; peach-flavored, 250 mg. (400,000 units) per 5-cc. teaspoonful. Supplied as vials of powder to make 40 cc. *Tablets*: 125 mg. (200,000 units) and 250 mg. (400,000 units) in vials of 36.

TABLETS

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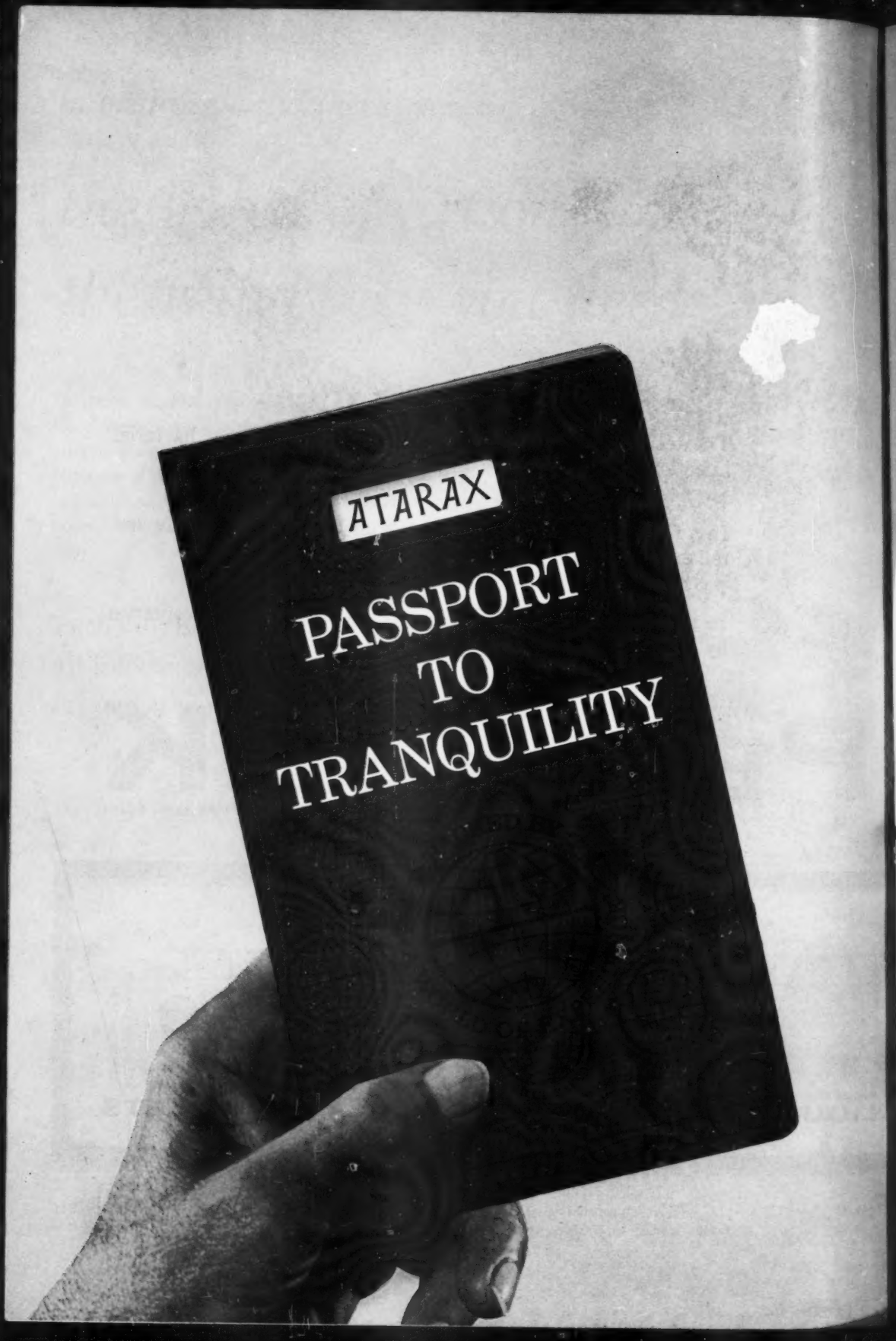
Philadelphia 1, Pa.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PASSPORT
TO
TRANQUILITY

Passport

☞ **a universal record of effectiveness**

In anxiety, tension and agitation, ATARAX "... produced a more favorable state of calm and tranquility than any drug previously used."[1]

☞ **widest latitude of safety and flexibility**

No serious adverse reaction ever documented – five dosage forms and sizes

☞ **chemically distinct among tranquilizers**

Not a phenothiazine or a meprobamate

☞ **added frontiers of usefulness**

These unique benefits in specific indications

ANTIHISTAMINIC
ANTIARRHYTHMIC
ANTISECRETORY

BACKED BY A WORLD OF EXPERIENCE

Dosage: ADULTS, one 25 mg. tablet, or one tbsp. Syrup q.i.d. CHILDREN – 3-6 years, one 10 mg. tablet or one tsp. Syrup t.i.d.; over 6 years, two 10 mg. tablets or two tsp. Syrup t.i.d.

Supplied: Tiny 10 mg., 25 mg., and 100 mg. tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.

References: 1. Farah, L.: Internat. Rec. Med. *169*:379 (June) 1956. 2. Smigel, J. O., et al.: J. Am. Geriatrics Soc. *7*:61 (Jan.) 1959. 3. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958. 4. Eisenberg, B. C.: J.A.M.A. *169*:14 (Jan. 3) 1959. 5. Maryssael, L.: Bruxelles-méd. *38*:141 (Jan. 26) 1958. 6. Pfleger, R.: Med. Klin. *53*:1030 (June 5) 1958. 7. Over 200 laboratory and clinical papers from 14 countries.

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PASSPORT TO TRANQUILITY

(brand of hydroxyzine)

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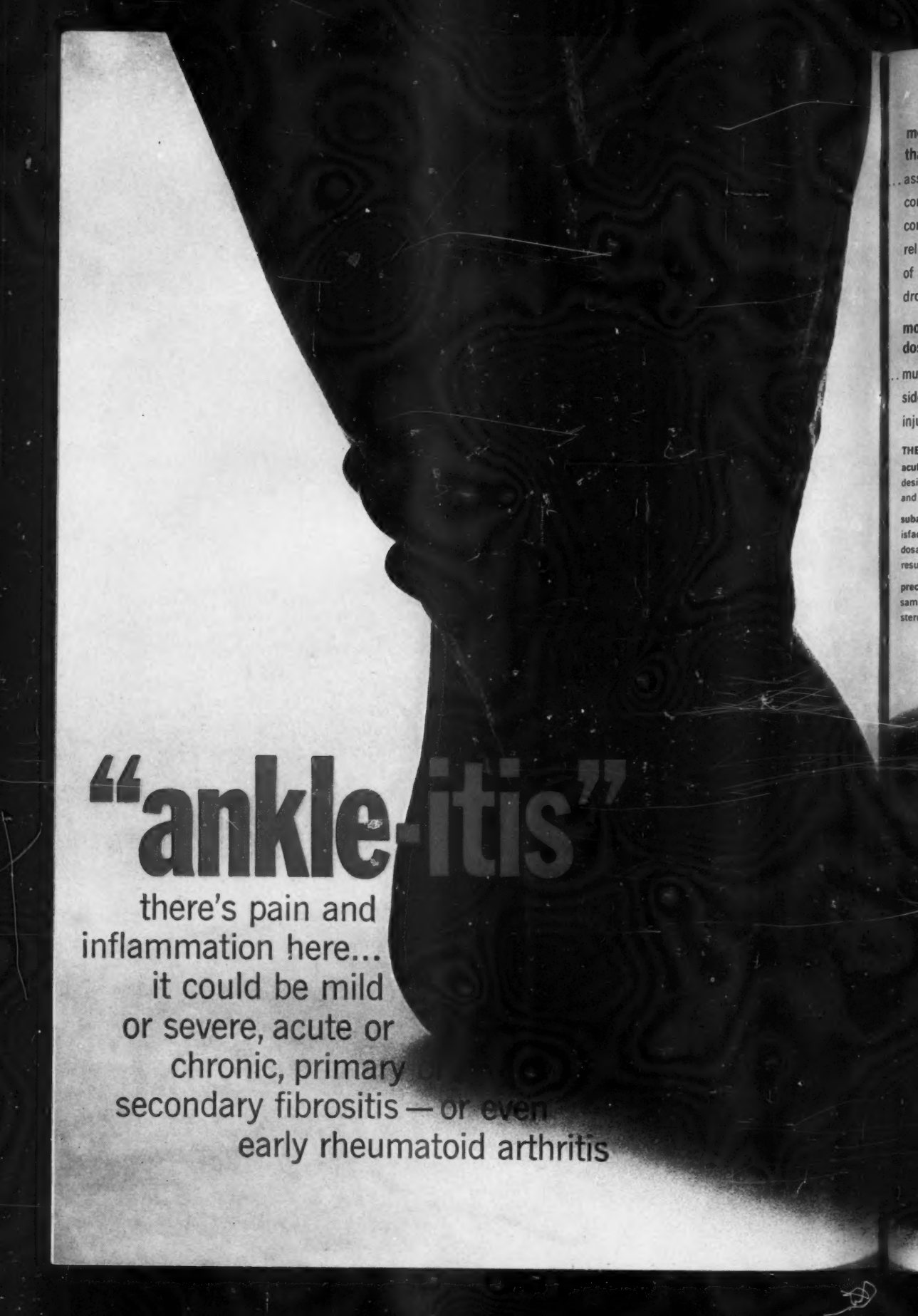
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being


"ankle-itis"
there's pain and
inflammation here...
it could be mild
or severe, acute or
chronic, primary
secondary fibrositis — or even
early rheumatoid arthritis

more potent and comprehensive treatment than salicylate alone

...assured anti-inflammatory effect of low-dosage corticosteroid[1] . . . additive antirheumatic action of corticosteroid plus salicylate[2-5] brings rapid pain relief; aids restoration of function . . . wide range of application including the entire fibrositis syndrome as well as early or mild rheumatoid arthritis

more conservative and manageable than full-dosage corticosteroid therapy—

...much less likelihood of treatment-interrupting side effects[1-6] . . . reduces possibility of residual injury . . . simple, flexible dosage schedule

THERAPY SHOULD BE INDIVIDUALIZED

acute conditions: Two or three tablets four times daily. After desired response is obtained, gradually reduce daily dosage and then discontinue.

subacute or chronic conditions: Initially as above. When satisfactory control is obtained, gradually reduce the daily dosage to minimum effective maintenance level. For best results administer after meals and at bedtime.

precautions: Because SIGMAGEN contains prednisone, the same precautions and contraindications observed with this steroid apply also to the use of SIGMAGEN.

in any case it calls for

Sigmagen®

corticoid-salicylate compound tablets

Composition

METICORTEN® (prednisone)	0.75 mg.
Acetylsalicylic acid	325 mg.
Aluminum hydroxide	75 mg.
Ascorbic acid	20 mg.

Packaging: SIGMAGEN Tablets, bottles of 100 and 1000.

References: 1. Spies, T. D., et al.: J.A.M.A. 159:645, 1955. 2. Spies, T. D., et al.: Postgrad. Med. 17:1, 1955. 3. Gelli, G., and Della Santa, L.: Minerva Pediat. 7:1456. 1955. 4. Guerra, F.: Fed. Proc. 12:326, 1953. 5. Busse, E. A.: Clin. Med. 2:1105, 1955. 6. Sticker, R. B.: Panel Discussion, Ohio State M. J. 52:1037, 1956.

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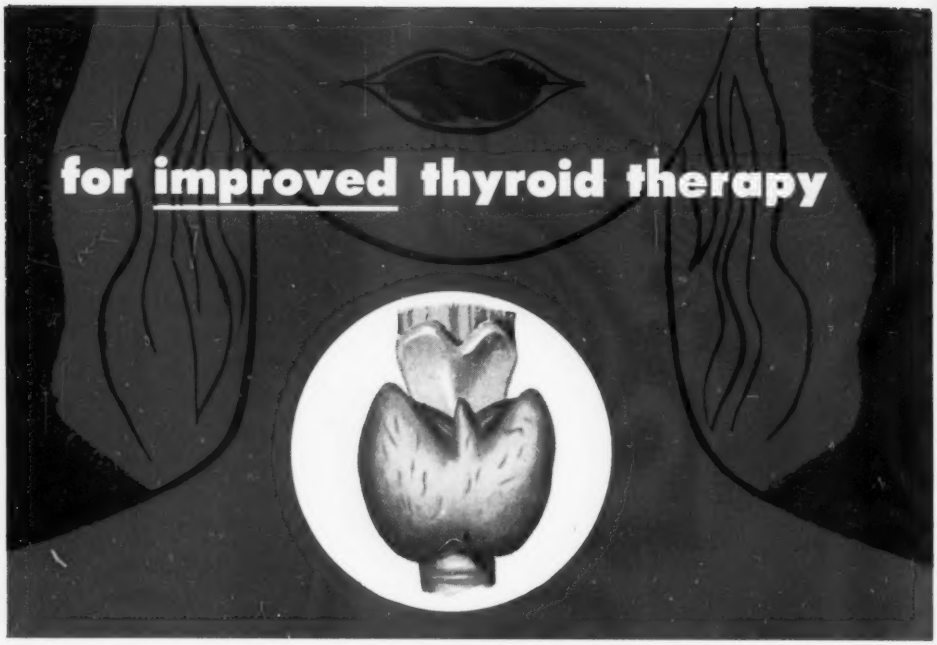

WARREN-TEED VITAROID TABLETS

Because safer and more effective hypothyroid therapy calls for more than thyroid substance alone, Vitaroid Tablets offer:

Natural Thyroglobulin — the most readily assimilable of thyroid substances.

Ascorbic Acid — to meet the greater demand of increased metabolic rate, and compensate for possible Vitamin C losses in vital tissues.

Thiamine (precursor of cocarboxylase, essential for metabolism of the thyroid substance) — to reduce likelihood of fading metabolic response and drug-induced neuritis.

Riboflavin and **Nicotinamide** — to balance the increased use of thiamine and cocarboxylase, and reduce or eliminate thyroid therapy nervousness.

Vitamin D — to minimize possibility of negative mineral balance with increased metabolism.

INDICATIONS:

Hypothyroidism or myxedema and the accompanying variety of thyroid deficiency complications. Often useful in treating physical and mental lassitude in patients exhibiting no organic disorder.

EACH TABLET CONTAINS:

Thyroid U.S.P.	30 mg. (½ gr.)
Vitamin D (Calciferol)	200 USP Units
Ascorbic Acid	15.0 mg.
Riboflavin	1.0 mg.
Thiamine HCl	3.0 mg.
Nicotinamide	5.0 mg.

DOSAGE:

The thyroid substance content of each Vitaroid Tablet (½ gr. USP) is the determining factor in establishing dosage.

THE WARREN-TEED PRODUCTS COMPANY

COLUMBUS 8, OHIO

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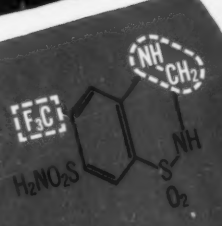
WARREN-TEED PHARMACEUTICALS

Improved molecular structure!
Higher sodium chloride excretion!



18-hour diuresis on a single 50-mg. tablet

saluron™ TABLETS

sustained-action hydroflumethiazide 'Bristol'

Demonstrated[1] to achieve—

30% MORE SODIUM EXCRETION
than maximally effective parenteral dosage of meralluride

62% MORE SODIUM EXCRETION
than maximally effective oral dosage of chlorothiazide

. . . with less risk of potassium and bicarbonate depletion

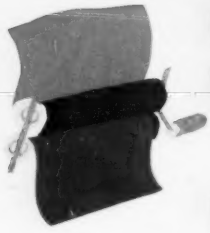
. . . with no significant serum electrolyte changes

Bristol

A RECORD OF PROGRESS

FIRST — chlorothiazide
NEXT — hydrochlorothiazide
THEN — flumethiazide
NOW — sustained-action hydroflumethiazide 'Bristol'

NOW...more efficient, sustained diuresis with a single 50 mg. tablet of this new and improved oral diuretic



SALURON

sustained-action hydroflumethiazide 'Bristol' TABLETS

clinical research findings

- Effective dose 50 mg. per day.[1-6]
- Prompt sodium excretion, with "a duration of at least 18 hours."[2]
- 30% **more** natriuresis than parenteral meralluride — 62% **more** than oral chlorothiazide.
- Less potassium and bicarbonate excretion or pH change than with chlorothiazide or hydrochlorothiazide.
- "No significant serum electrolyte changes."[2]
- Continued effectiveness with prolonged use.[1,2,4,5,6]
- Well tolerated.[1-6]

INDICATIONS:
SALURON is indicated for the treatment of salt and water retention associated with cardiac or renal insufficiency, hepatic cirrhosis, pregnancy, premenstrual syndrome, or steroid administration.

DOSAGE:
Usual dose one tablet on arising. Some patients respond to as little as 25 mg per day; but doses as high as 400 mg. may be used. Ideally, the dosage should be adjusted to the individual patient's need, so that effective diuresis is produced with the minimal dose.

SUPPLY:
Scored 50 mg. tablets of sustained-action hydroflumethiazide; bottles of 50

Comprehensive information on administration, dosage and precautions on package insert, or available on request.

REFERENCES:

1. Dube, A. C., Van Duyn County Hospital, Onondaga, N. Y.: Personal communication.
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CHLOR-TRIMETON® REPETABS, 8 and 12 mg.
Chlorprophenpyridamine Maleate

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Chlor-Trimeton plus phenylephrine

symbol of the one-dose convenience you want for your patient

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PROMPT REPETAB RELIEF • ALL DAY OR NIGHT • ASSIS

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The FILIBON jar is a handsome and handy reminder for everyday prenatal nutritional support. You can be sure she will be reminded of her FILIBON-a-day... and that the up-to-the-minute formula covers nutritional defenses throughout pregnancy.

FILIBON provides ferrous fumarate, an iron well-tolerated by even the most easily upset patients. Each small, dry-filled capsule also includes vitamin K and AUTRINIC® Intrinsic Factor Concentrate that enhances, never inhibits, B_{12} absorption. For complete formula see Physicians' Desk Reference, page 688.

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Phosphorus-free FILIBON® Prenatal Capsules Lederle

safely control the "target symptoms" of emotional stress with the smallest effective dosage (0.25 mg. b.i.d.) of any neuroleptic* agent

the promise of

PERMITIL®

Fluphenazine dihydrochloride

in everyday office practice

Primer on PERMITIL

Q. Why another psychopharmacologic agent?

A. The ever-expanding role of chemistry in the treatment of mental and emotional problems in this new era of psychopharmacologic drugs is amply attested to by the growing number of rauwolfia, mephenesin, diphenylmethane and phenothiazine derivatives now in clinical use. When one considers the wide range of indications to be treated—from severe psychosis to mild situational stress—it becomes somewhat clearer as to the reason for the number and diversity of drugs available. In addition, improvements and refinements of existing agents are constantly taking place. Drugs tailored to perform a selected, single function are emerging. So it is with PERMITIL.

Q. Why another phenothiazine?

A. All members of this group contain a phenothiazine nucleus and a side chain attached to the nitrogen atom. Differences in potency are related to specific chemical alterations in these compounds. Clinical evidence demonstrates that the phenothiazines act principally, but to varying degrees, on several subcortical areas of the brain. Thus, certain of these drugs produce sedation and potentiate the action of barbiturates, while others do not; autonomic side effects (such as blurred vision, constipation) are produced by some and not by others; some have been shown to be very effective antiemetic agents. At certain dosage levels, the phenothiazine derivatives also may cause extrapyramidal side effects. These, however, are neuropharmacologic rather than toxic effects and are totally reversible.

Since there is a correlation between the dosage of a phenothiazine derivative and the frequency and the type of side effects it causes, ***the less of the drug needed to achieve therapeutic results, the less likely are serious side effects.*** **Thus, the lower the effective dosage of a phenothiazine derivative, the lower the incidence of unwanted side reactions and, conversely, the higher the level of therapeutic response.**

For these reasons, the search has been unceasing to develop a phenothiazine with an optimum therapeutic ratio.

Q. What is a "neuroleptic" agent?

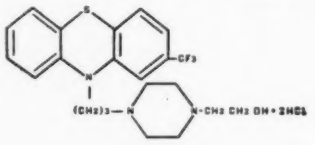
A. The term "neuroleptic" implies a specific effect of a pharmacologic agent on the nervous system. It refers to a mode of action on specific subcortical areas which strongly influence emotional behavior in contradistinction to hypnotic agents which dull the senses. Neuroleptics achieve control of anxiety symptoms without inducing either somnolence or euphoria. Thus, there is an increase in the patient's capacity to cope with life's problems more successfully. The terms "tranquilizers" and "ataraxics" are descriptively impressive, but they fail to convey what seems pharmacologically unique.

Q. Why introduce the term "neuroleptic"?

A. Because it has a precise psychopharmacologic meaning and is more descriptive of the action of PERMITIL than any other current term.

Q. What is PERMITIL?

A. PERMITIL is a new anti-anxiety agent of extraordinary potency and effectiveness. Chemically, PERMITIL is 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine dihydrochloride. The structural formula is:

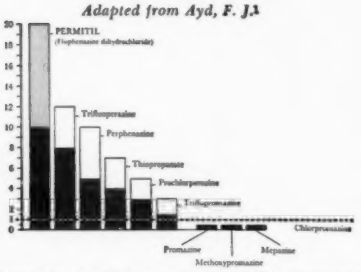


Q. Why is PERMITIL unique?

A. Although PERMITIL can be broadly classified as a phenothiazine, it exhibits a spectrum of unique effects at unprecedented low dosage—a feature that markedly distinguishes this compound from other anti-anxiety drugs.

The Relative Therapeutic Potency of Various Phenothiazines

Adapted from Ayd, F. J.[1]



The potency of each drug was determined by the criteria proposed by Freyhan.[2] These were: *(1)* the attainable level of psychomotor inhibition, *(2)* the speed of action, and *(3)* the dosage required to obtain effective action.

Q. What are the distinctive clinical advantages of PERMITIL?

A. Extensive clinical studies have established important psychopharmacologic advantages for PERMITIL.

1. The effective dosage of PERMITIL *(0.25 mg.* b.i.d.) is the lowest safe dosage of any antianxiety agent. Since fractional milligram doses of PERMITIL usually produce a therapeutic effect, many of the annoying side effects of the other phenothiazines, which are dose-related, occur less frequently or not at all. In fact, any side effects associated with dosage not exceeding 1 mg. per day have been uncommon and transitory. PERMITIL represents an advance over its predecessors[1] because of its higher level of therapeutic response and low order of side reactions.

2. Unlike other phenothiazines, PERMITIL alleviates symptoms of anxiety, tension, agitation and emotional unrest *without* depressant effect, impaired alertness or slowed intellectual function. Furthermore, anxiety-induced symptoms of apathy, indifference, listlessness, reduced initiative and chronic emotional fatigue (often refractory to other phenothiazines) frequently respond to administration of PERMITIL. Thus, a significantly wider spectrum of "target symptoms" amenable to therapy is an outstanding property of PERMITIL.

3. Onset of action is rapid and patients soon become more relaxed and less tense. The patient regains a more confident outlook and normal drive is restored.

4. PERMITIL has an inherently long duration of effect. This makes possible a particularly convenient and easy-to-remember schedule of morning and evening dosage.

Q. For what, specifically, is PERMITIL indicated?

A. PERMITIL is indicated for the control of the "target symptoms" of emotional stress so common in everyday office practice. The basic areas of usefulness for PERMITIL are: (1) behavioral disturbances characterized by anxiety, tension, apprehension and instability, as well as depressive symptoms associated with anxiety states; (2) emotional stress accompanying organic disorders and complicating recovery from, or acceptance of, the underlying condition; (3) chronic disorders in which anxiety and stress are contributing factors, e.g., gastrointestinal dysfunctions, neurodermatitis, asthma, premenstrual tension, arthritis, hypertension and tension headache.

Q. Is the dosage schedule, as with many phenothiazine derivatives, complex and complicated?

A. No. PERMITIL has an inherently long duration of effect so that twice-a-day dosage provides the patient with day and night symptom alleviation. The lowest dose of PERMITIL that will produce the desired clinical effect should be used. *The recommended dose for most adults is one 0.25 mg. tablet twice a day.* This may be increased to two 0.25 mg. tablets twice a day if required. Total daily dosage in excess of 1 mg. should be employed only in patients with relatively severe symptoms who have had a trial of lower dosages first that were well tolerated but were only partially effective. In such patients, the total daily dose may be increased to a maximum of 2 mg., given in divided amounts. (Dosage for children has not been established.)

Q. What about side effects and contraindications to PERMITIL?

A. At the recommended dosage of PERMITIL, side effects have been observed infrequently or not at all. PERMITIL, as with other phenothiazines, is contraindicated in severely depressed states.

Q. How is PERMITIL supplied?

A. PERMITIL is available as Tablets, 0.25 mg., bottles of 50 and 500.

References: 1. Ayd, F. J.: The current status of major tranquilizers, in press. 2. Freyhan, F. A.: Therapeutic implications of differential effects of new phenothiazine compounds, Am. J. Psychiat. 115:577-585 (Jan.), 1959.

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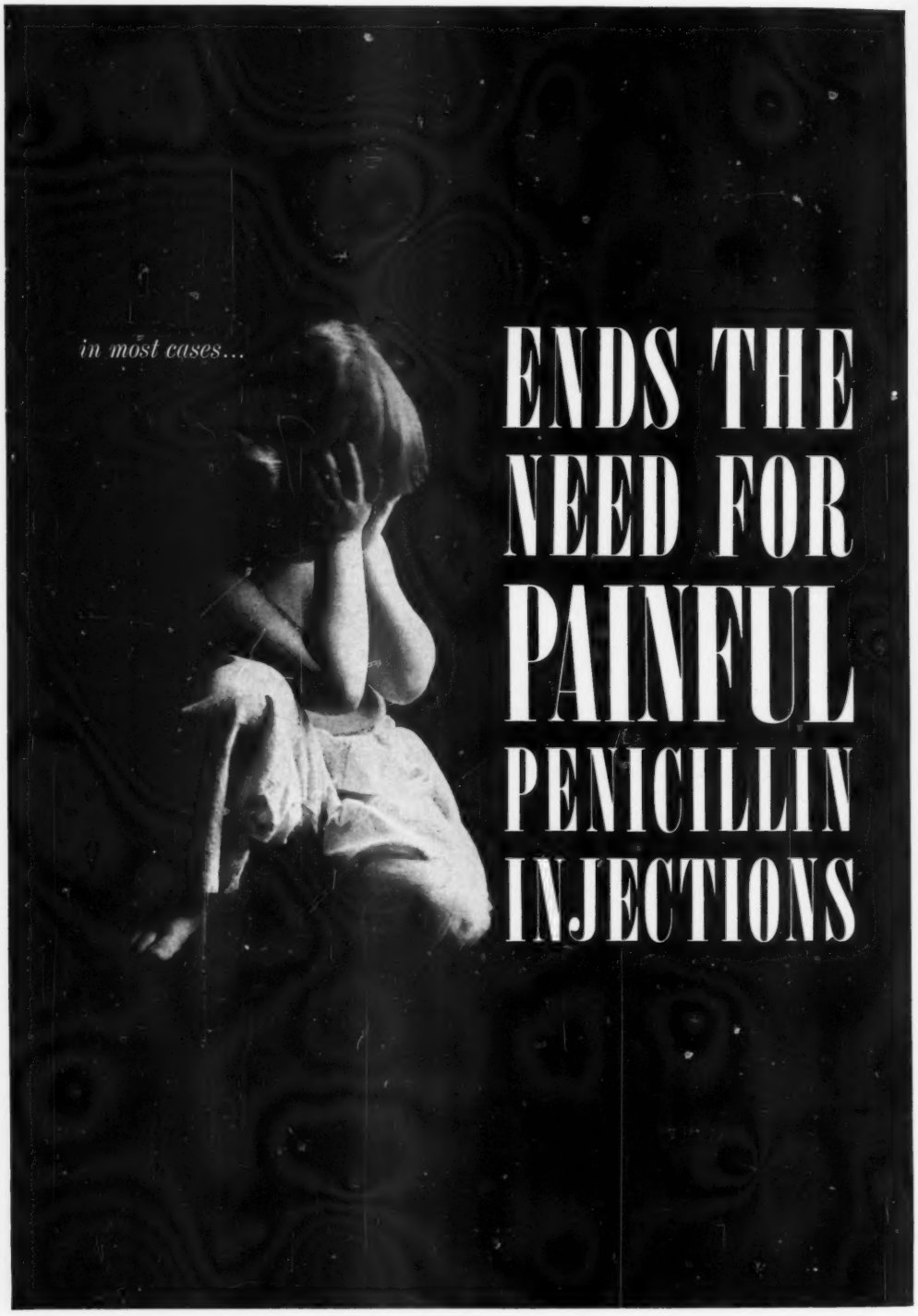
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ENDS THE NEED FOR PAINFUL PENICILLIN INJECTIONS

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Now, with Compocillin-VK, patients get blood levels as fast and as high as with intramuscular procaine penicillin. And in most cases, you'll find clinical results are every bit as good as with the injectable. ■ Compocillin-VK may be used whenever oral penicillin therapy is indicated. Dosage range is from 125 mg. (200,000 units) three times daily to 250 mg. (400,000 units) every four hours. Children's dosage is determined by body weight ■ Compocillin-VK Filmtabs 125 mg. (200,000 units), bottles of 50 and 100; 250 mg. (400,000 units), bottles of 25 and 100. Compocillin-VK Granules for Oral Solution come in 40-cc. and 80-cc. bottles. When reconstituted, each 5-cc. teaspoonful represents 125 mg. (200,000 units) of potassium penicillin V.

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in tiny, easy-to-swallow Filmtabs® in tasty, cherry-flavored Oral Solution

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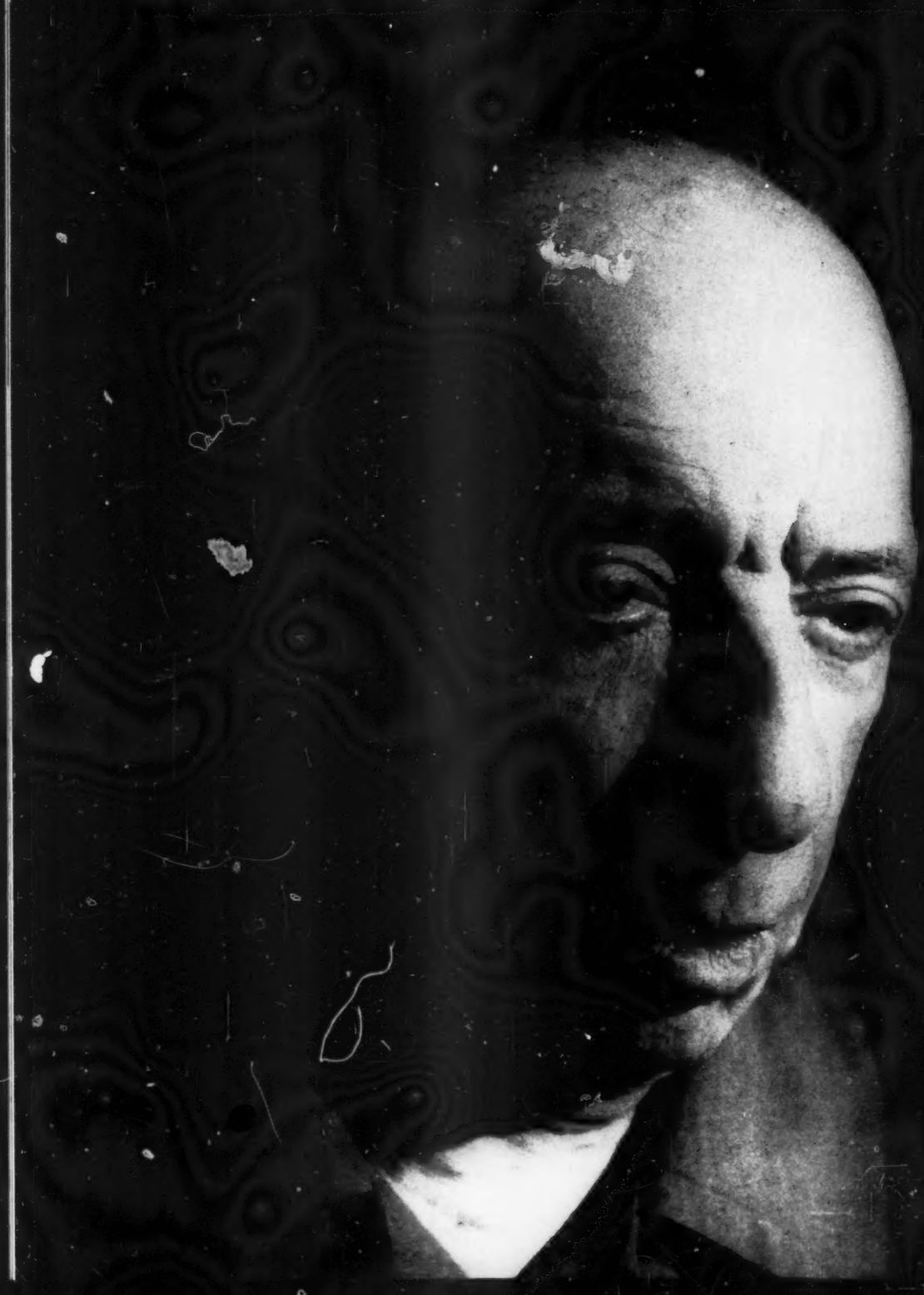
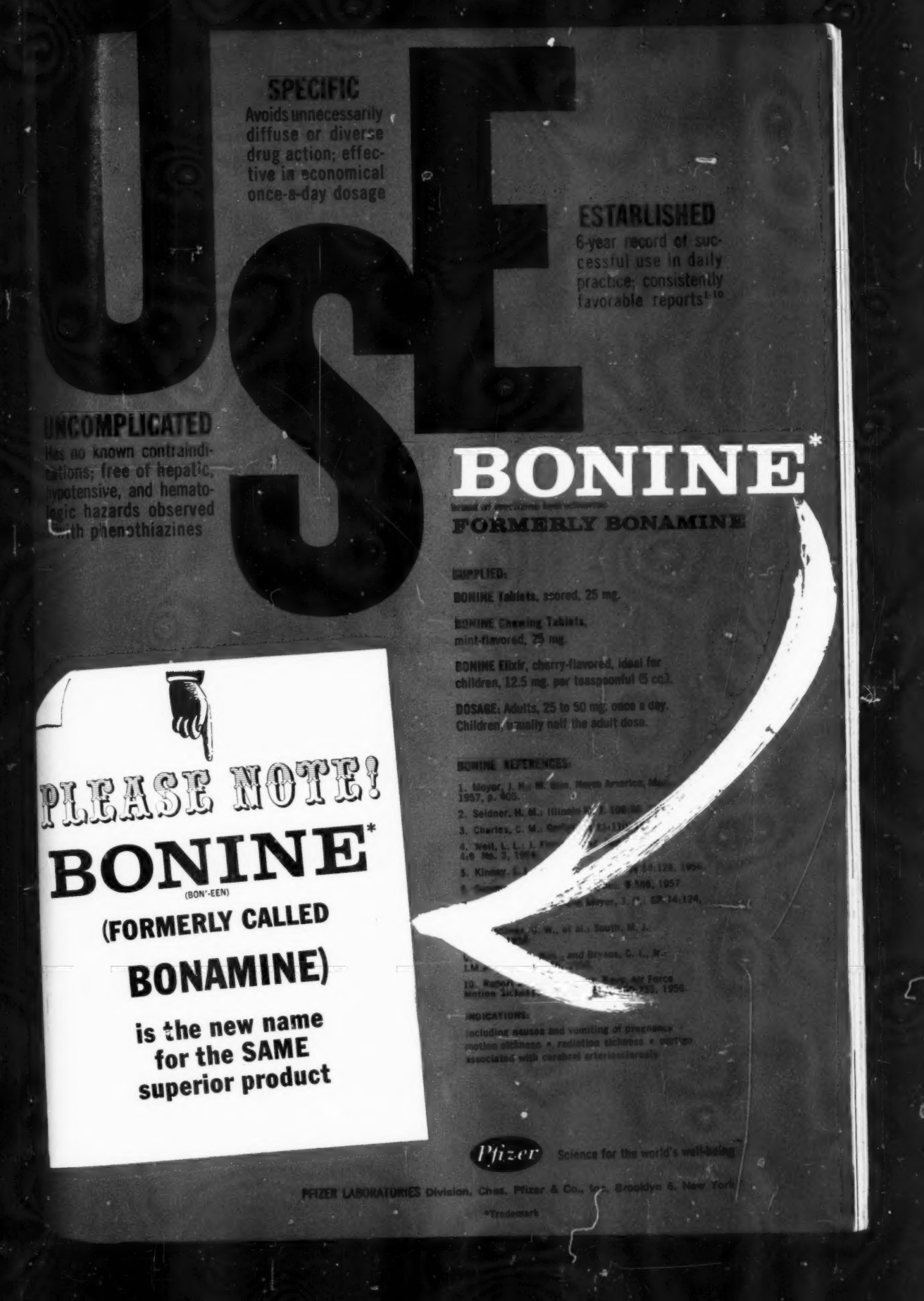
IN NAUSEA/VOMITING/VERTIGO




USE
SPECIFIC
Avoids unnecessarily diffuse or diverse drug action; effective in economical once-a-day dosage
ESTABLISHED
6-year record of successful use in daily practice; consistently favorable reports[1-10]
UNCOMPLICATED
Has no known contraindications; free of hepatic, hypotensive, and hematologic hazards observed with phenothiazines
BONINE*
FORMERLY BONAMINE
SUPPLIED:
BONINE Tablets, scored, 25 mg.
BONINE Chewing Tablets, mint-flavored, 25 mg.
BONINE Elixir, cherry-flavored, ideal for children, 12.5 mg. per teaspoonful (5 cc.).
DOSAGE: Adults, 25 to 50 mg. once a day. Children, usually half the adult dose.
BONINE REFERENCES:
INDICATIONS:
including nausea and vomiting of pregnancy
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BONINE*
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Overwhelming evidence[1-13] proves:

HIGH-DOSAGE NICOTINIC ACID EFFECTIVELY LOWERS CHOLESTEROL LEVELS

WITHOUT DIETARY RESTRICTIONS[1,2]

VASTRAN® FORTE

capsules

In a recent report[1] on 44 patients, **VASTRAN FORTÉ** reduced plasma cholesterol levels to normal in 21 patients and lowered cholesterol levels by at least 40% in 14 more patients during a 30-week period. *There was no change in diet.*

VASTRAN FORTÉ produces no significant side effects on long-term administration. "No toxic reactions have been found by clinical and laboratory observations, including a battery of seven tests of hepatic function and needle biopsies of the liver in 17 patients after one year of therapy."[1] However, patients must be told to expect pronounced warm flushing within approximately 15 minutes of the early doses. This effect is the normal initial response to high-dosage nicotinic acid, and is in no way harmful. It generally does not occur after one or two weeks.

VASTRAN FORTÉ contains anticholesterol dosage of nicotinic acid[1-13] fortified by added B-complex factors to guard against vitamin deficiencies due to large dosage of a single B factor;[14-15] plus pyridoxine to improve utilization of unsaturated fatty acids in normal diets[16-17] and ascorbic acid[18] for support against degenerative arterial changes.

Each VASTRAN FORTÉ Capsule contains: nicotinic acid, 375.0 mg.; ascorbic acid, 50.0 mg.; riboflavin, 2.5 mg.; thiamine mononitrate, 5.0 mg.; pyridoxine hydrochloride, 0.5 mg.; calcium pantothenate, 2.5 mg.; cobalamin concentrate (vitamin B_{12} activity), 10.0 mcg. **Dosage:** Initial Dosage—2 capsules four times a day after meals for twelve weeks. Thereafter dosage should be adjusted according to response. Maintenance requirements may vary from 1 capsule q.i.d. to 4 capsules q.i.d. **Supply:** Bottles of 100.

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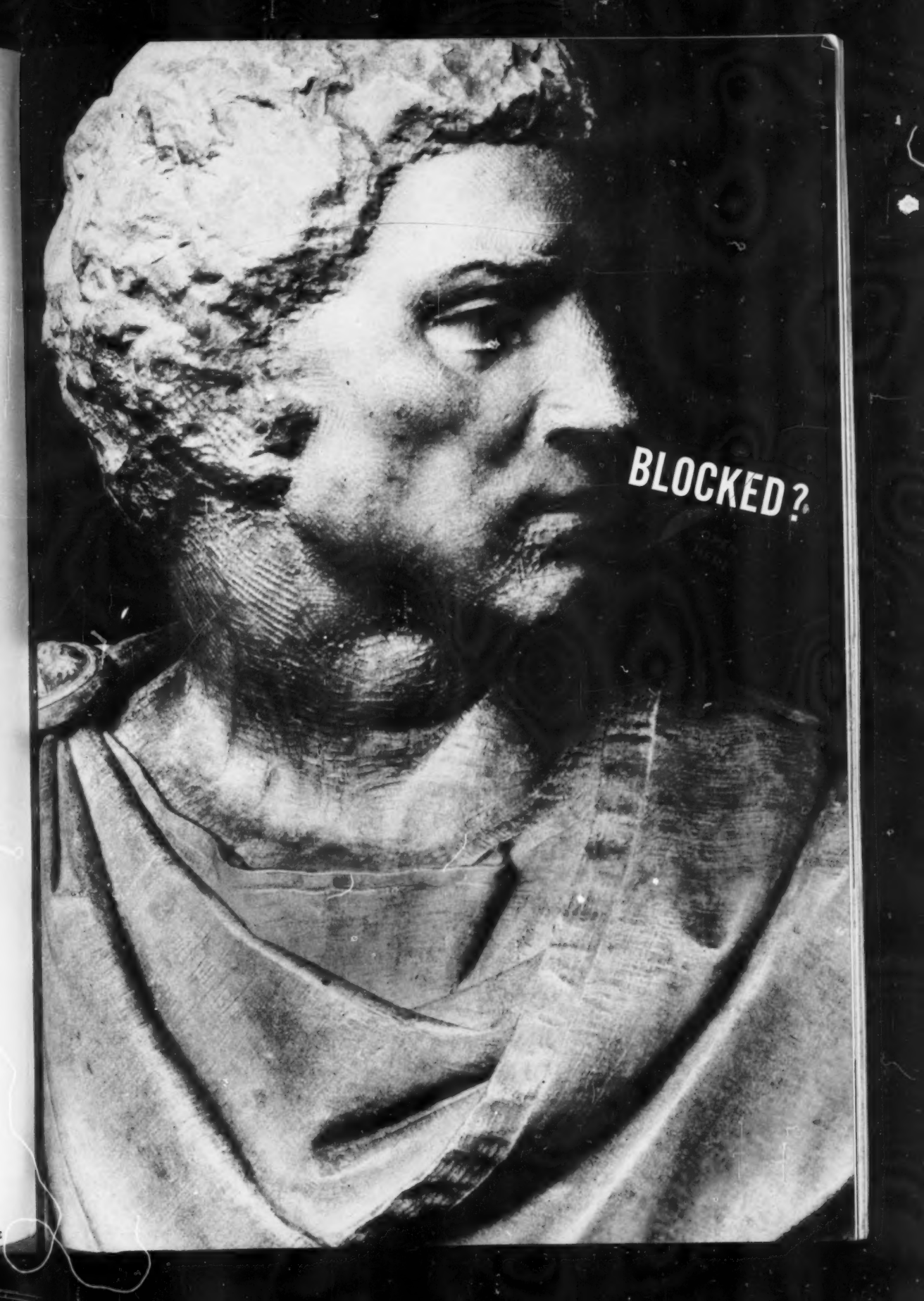
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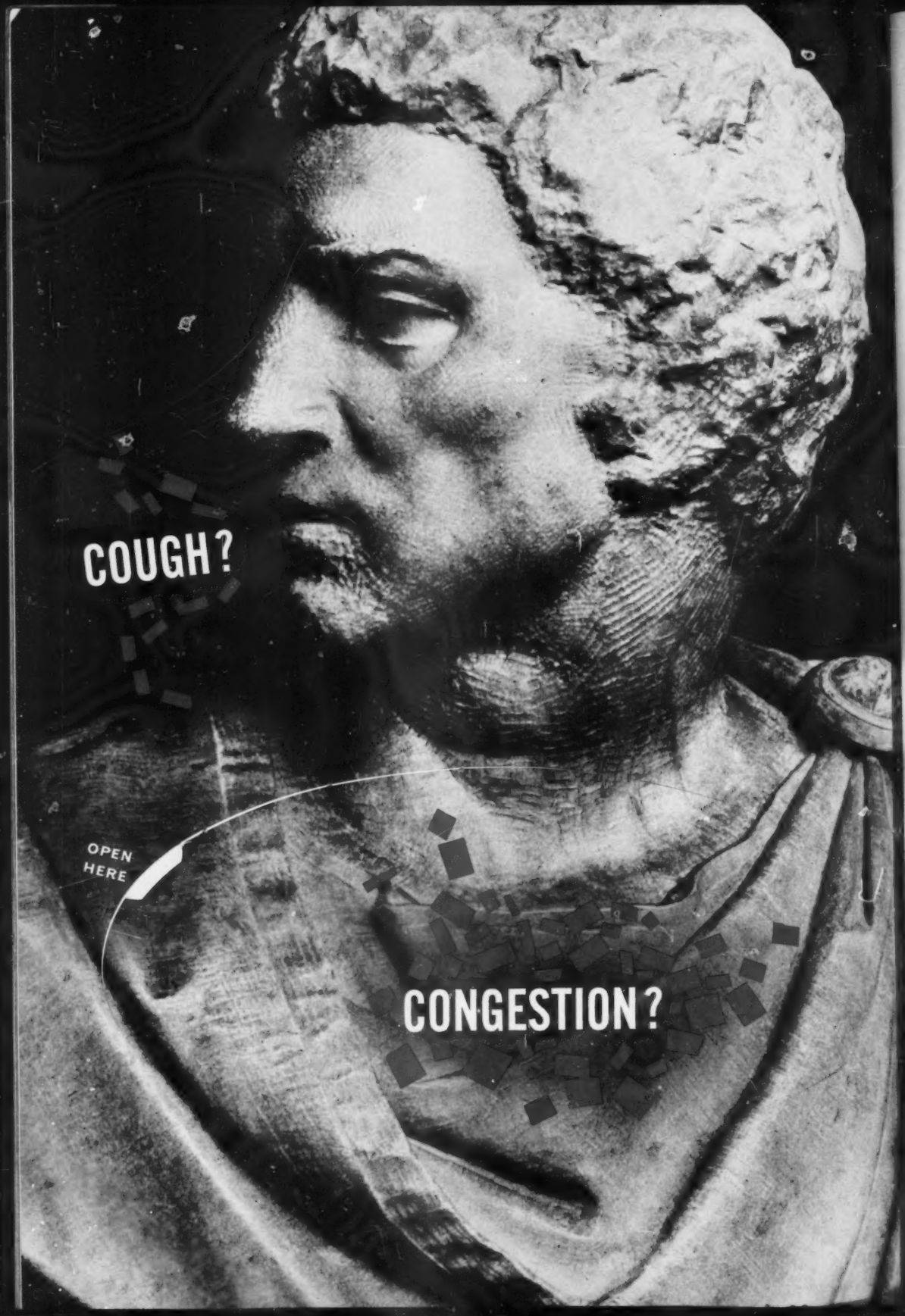
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An analgesic capable of replacing morphine and morphine-like synthetic agents in the widest range of clinical applications

NUMORPHAN* **provides: more satisfactory pain relief than morphine/effective in much smaller doses than morphine (1/10 the morphine dosage) / more rapid onset of action—10-20 minutes after administration / more prolonged duration of effect—lasts about 6 hours / marked freedom from side effects—respiratory depression, nausea, and constipation are rare / increased scope of pain relief in short- and long-term therapy / no "plateau effect": in ultrasevere pain, increasing the dose will ensure thorough analgesia / greater margin of safety and increased comfort for the patient**

SUPPLIED: In 10 cc. multiple-dose vials, 1.5 mg. 4-14-hydroxydihydromorphinone hydrochloride per cc. and as ampuls, 1 cc. and 2 cc., 1.5 mg. per cc. Rectal suppositories, 2 mg. and 5 mg. May be habit-forming.

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"A NEW ERA IN PAIN RELIEF"

clinically tested for 5 years/evaluated in 120 U. S. hospitals/over a quarter of a million doses given/ more than 25,000 patients treated

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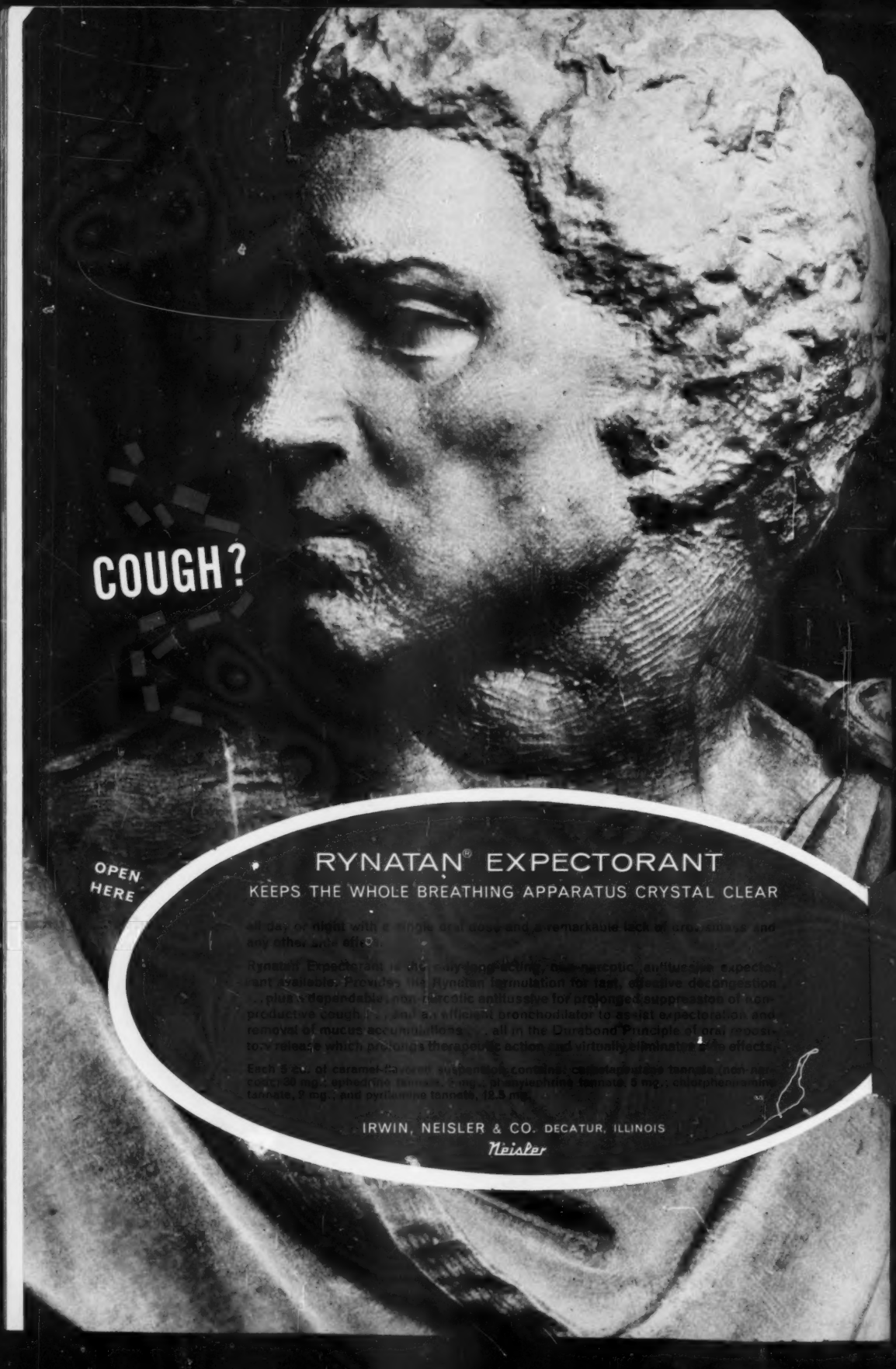
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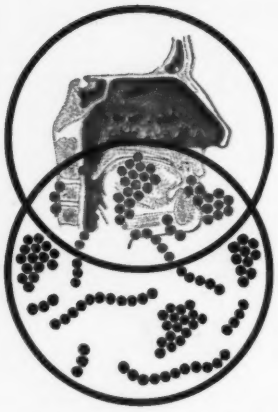
controls cough for hours
alleviates congestion
all day/all night



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- for the patient ill with congestion and infection of the upper respiratory tract, as in purulent rhinitis, sinusitis, tonsillitis and otitis media, when caused by sulfa-susceptible bacteria;
- because secondary invasion by such bacteria so frequently follows the common cold.[1]

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Triaminic and triple sulfas are not only pharmacologically *compatible*, they are a therapeutically *logical* combination for upper respiratory infections: Triaminic for effective decongestant relief from rhinitis, rhinorrhea and sinusitis;[2] triple sulfas for well-established antibacterial action.

The advantages of Trisulfaminic in upper respiratory infections include: proved effectiveness; safety; economy; ease of administration; less likelihood of sensitivity reactions;[3] compatibility with antibiotics and other antibacterial therapy. Provided also as Suspension for additional convenience.

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Each easy-to-swallow Trisulfaminic Tablet or 5 ml. teaspoonful of Suspension provides:

Triaminic® .....25 mg.
(phenylpropanolamine HCl 12.5 mg.
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Dosage:

Adults—2 to 4 tablets or tsp. initially, followed by 2 tablets or tsp. every 4 to 6 hours until the patient has been afebrile 3 days. *Children 8 to 12* — 2 tablets or tsp. initially, followed by 1 tablet or tsp. every 6 hours. *Children under 8*—dosage according to weight.

The palatability, convenience and effectiveness of the Suspension make it especially suitable for children and for those older patients who prefer liquid medication.

References: 1. Cecil, R. L., et al.: J.A.M.A. 124:8 (Jan. 1) 1944. 2. Fabricant, N. D.: E.E.N.T. Monthly 37:460 (July) 1958. 3. Beckman, H.: Drugs, Their Nature, Action & Use, Saunders, Philadelphia, 1958, p. 527.

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Miltown—Wallace ..... Facing A-134; A-182
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Equanitrate—Wyeth A-9
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Rautrax—Squibb A-188
Serpasil-Esidrix—Ciba A-17
Singoserp—Ciba A-186

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Ramses—Schmid A-87-126

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Diaparene—Homemakers Products A-218
Fulvicin—Schering A-7
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Mycolog—Squibb A-19
NeoDecadron—Merck Sharp & Dohme A-68-69
Neosporin—Burroughs Wellcome A-86
Ointment—Desitin A-89
Polysporin—Burroughs Wellcome A-86
Selsun—Abbott ..... Facing A-88

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Glutavene-K—Crookes-Barnes A-96

Diagnostic Aids
GG Test—Hyland A-98

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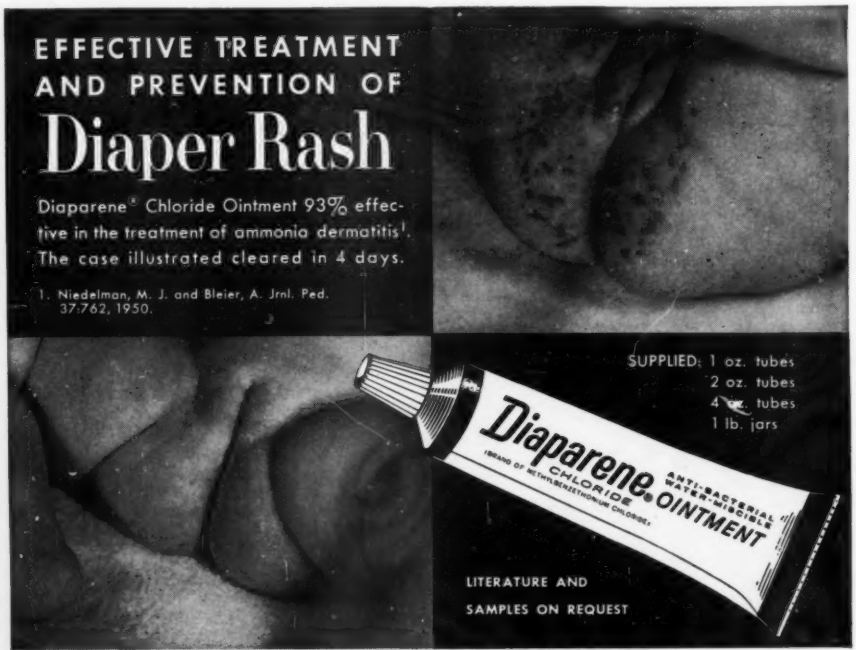
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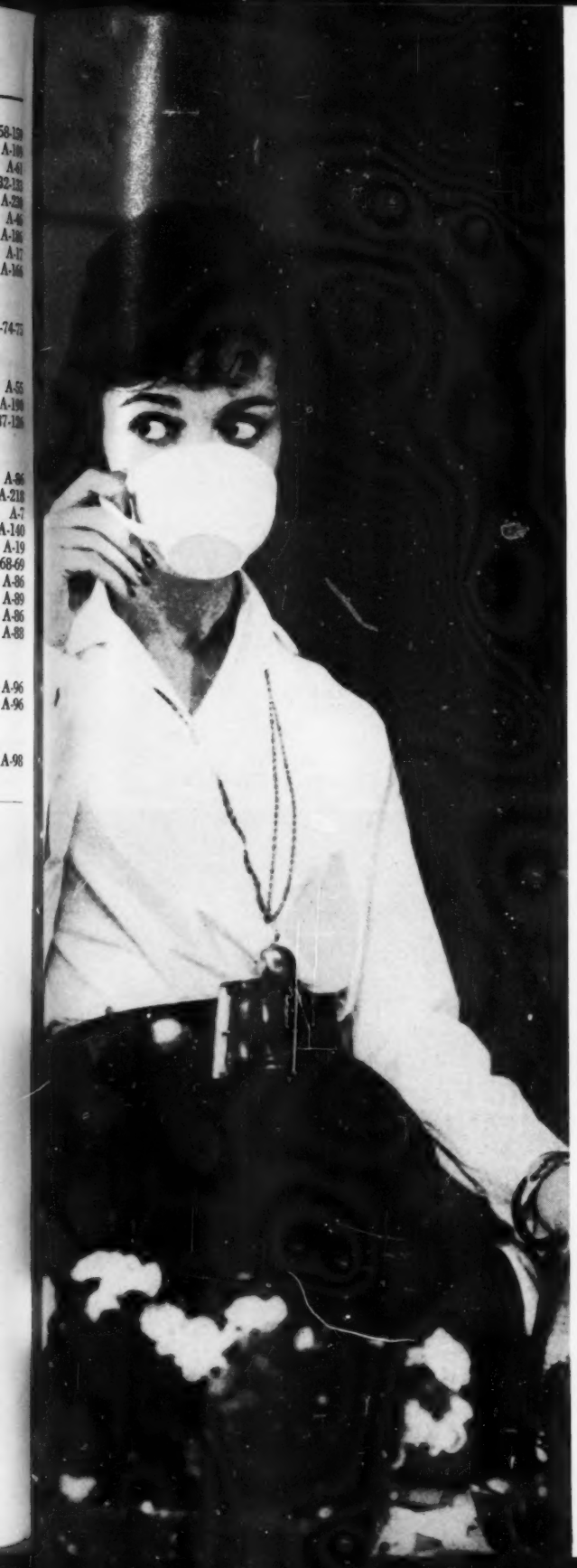

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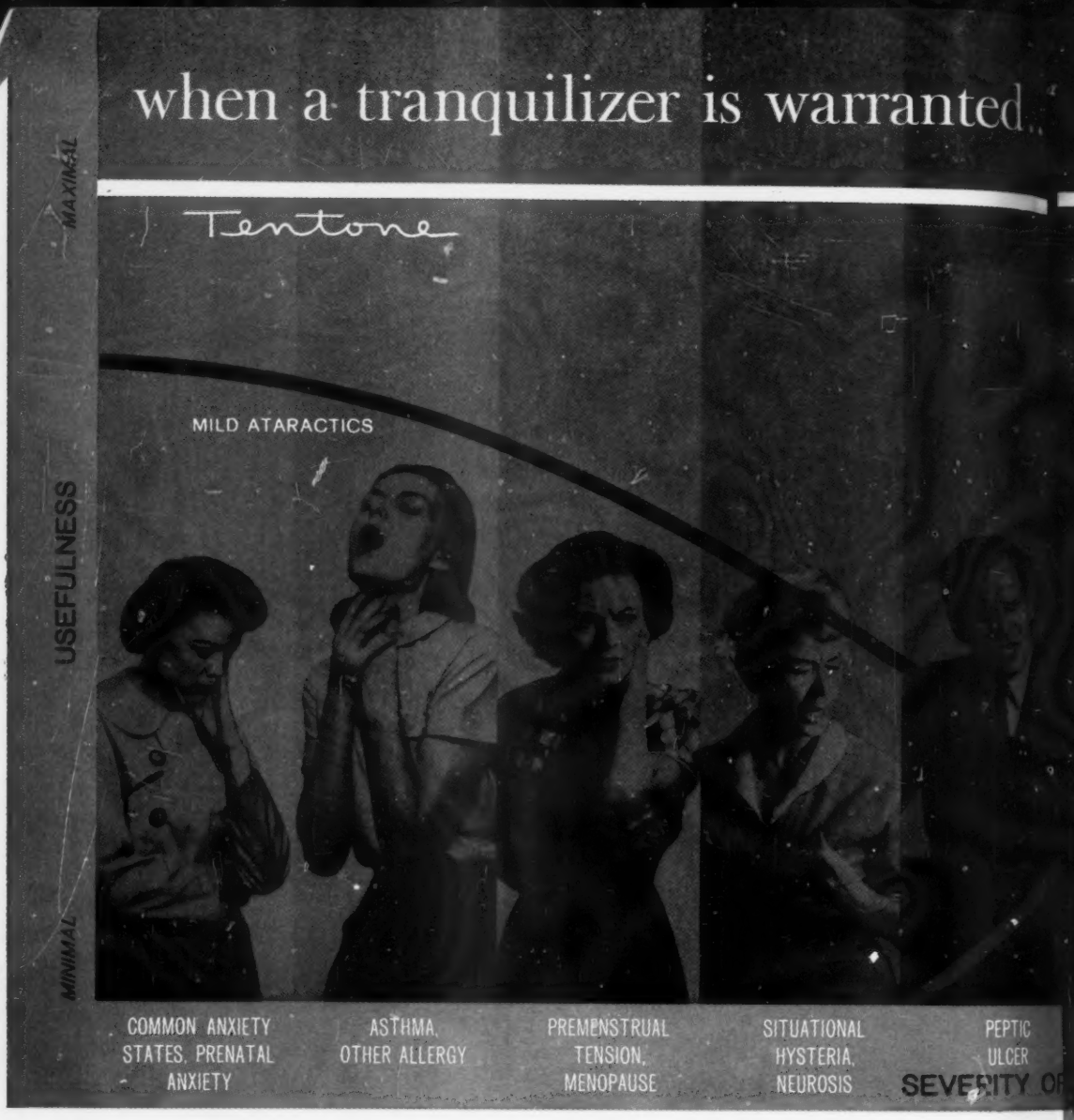

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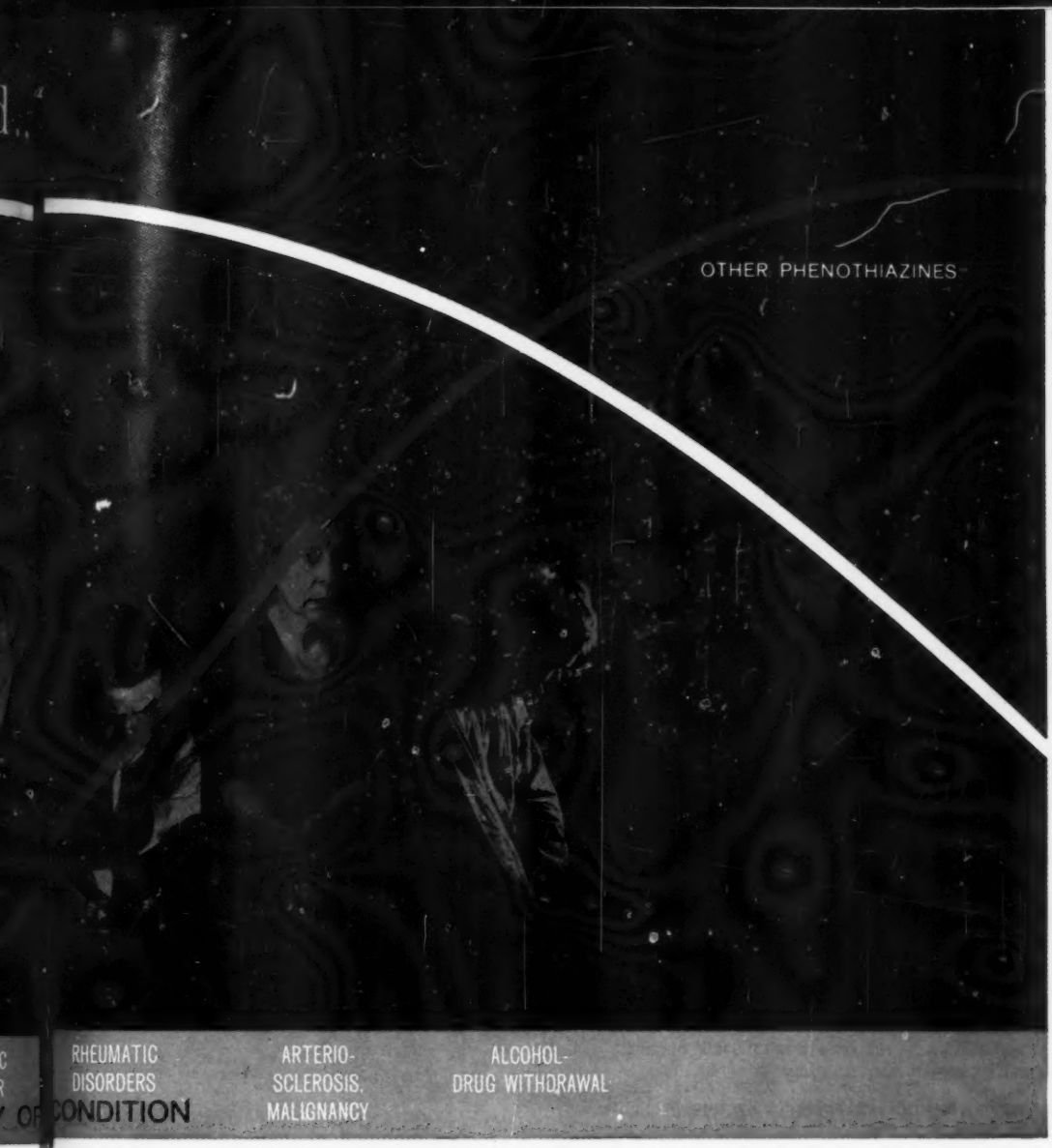

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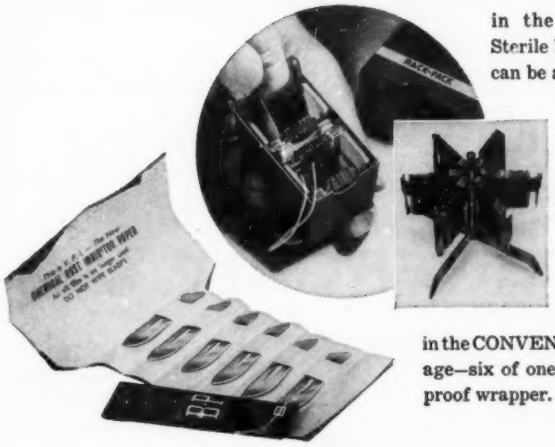

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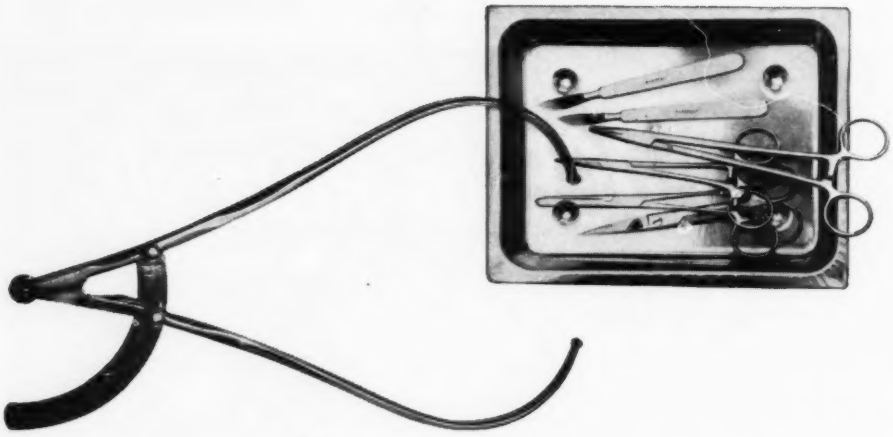

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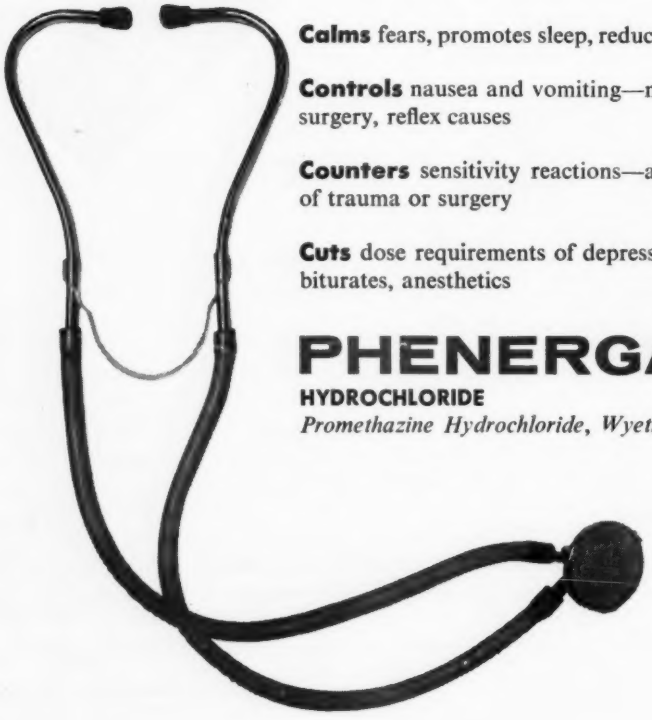

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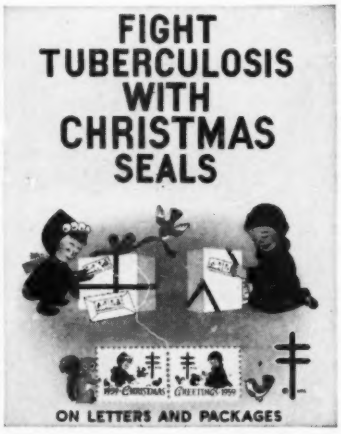

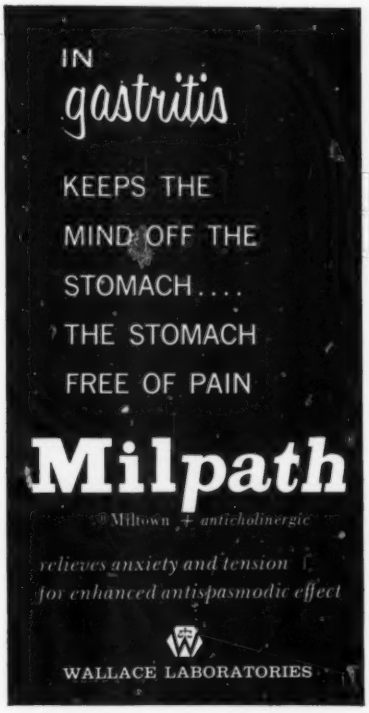

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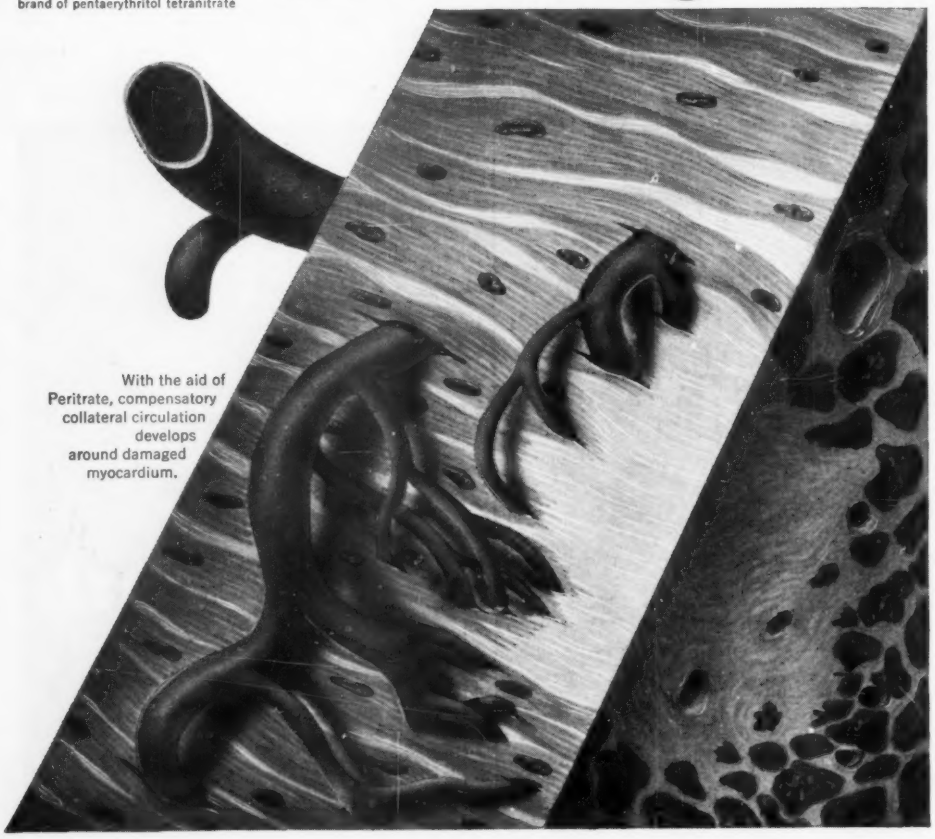

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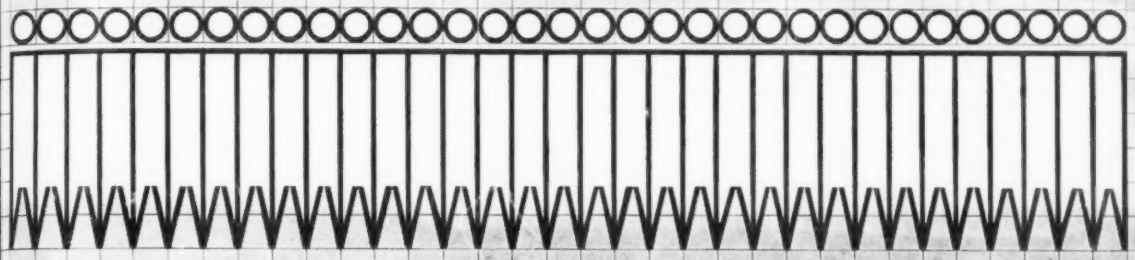
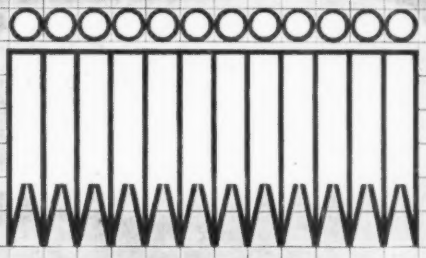
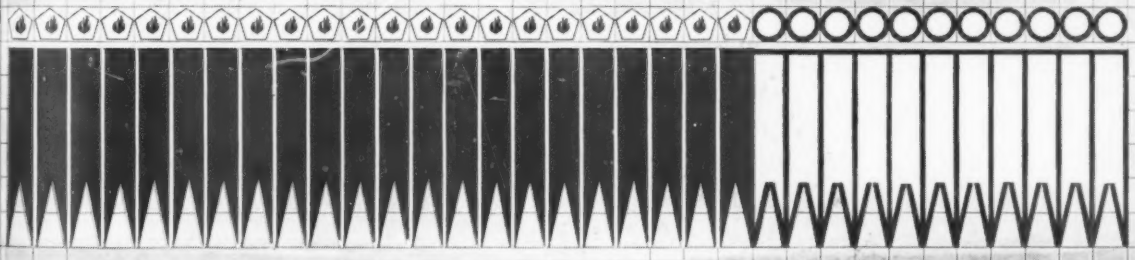


Of 45 arthritic patients who were refractory to other corticosteroids*





22 were successfully treated with **Decadron**[1,2]

1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

*Cortisone, prednisone and prednisolone.

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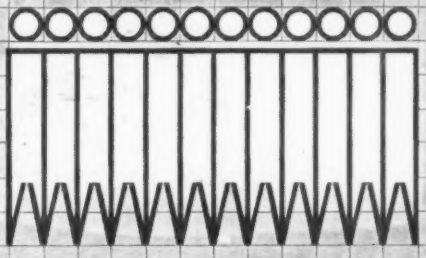
Additional information on DECADRON is available to physicians on request.



Merck Sharp & Dohme

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

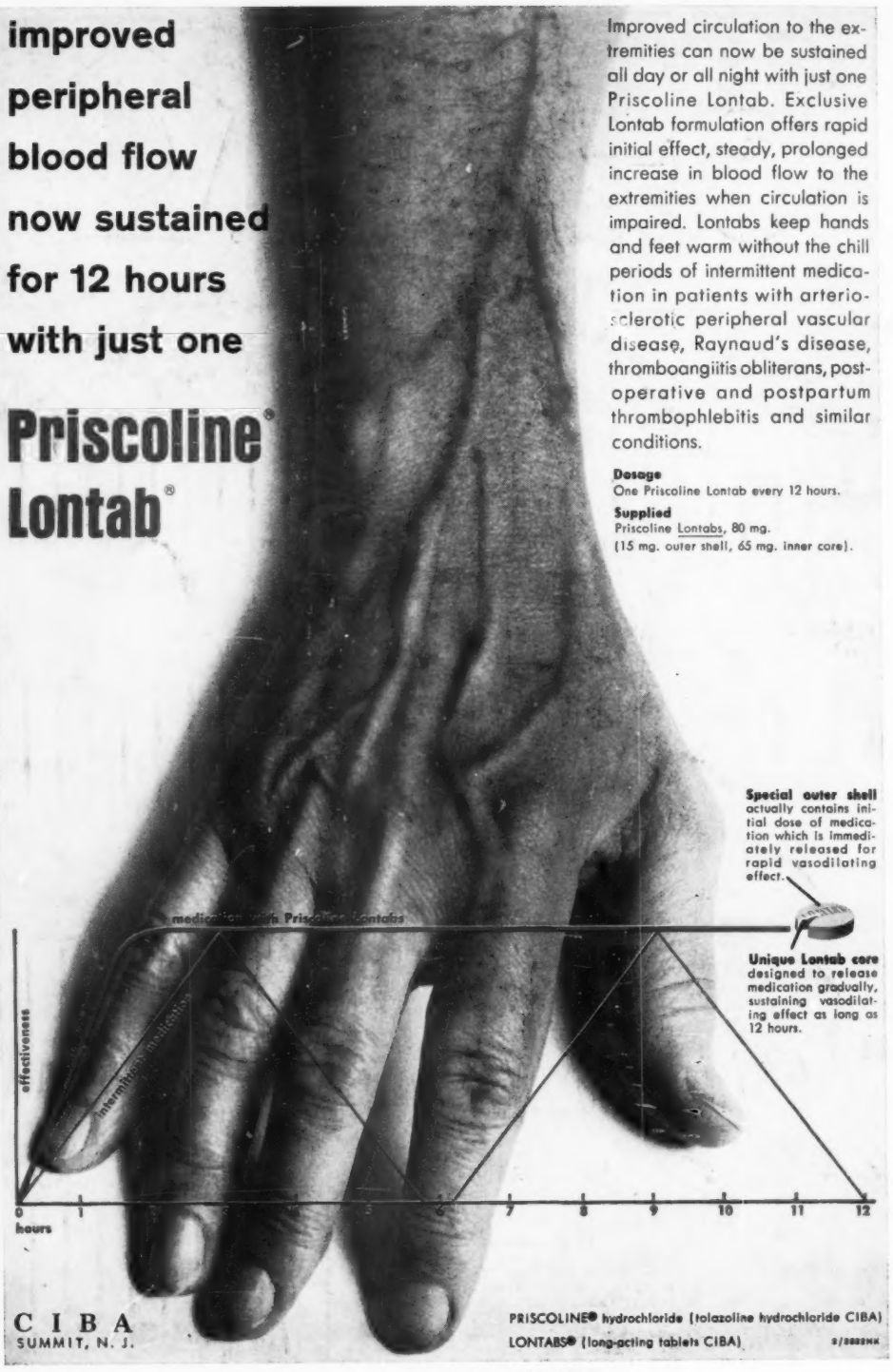
improved peripheral blood flow now sustained for 12 hours with just one

Priscoline® Lontab®

Improved circulation to the extremities can now be sustained all day or all night with just one Priscoline Lontab. Exclusive Lontab formulation offers rapid initial effect, steady, prolonged increase in blood flow to the extremities when circulation is impaired. Lontabs keep hands and feet warm without the chill periods of intermittent medication in patients with arteriosclerotic peripheral vascular disease, Raynaud's disease, thromboangiitis obliterans, postoperative and postpartum thrombophlebitis and similar conditions.

Dosage
One Priscoline Lontab every 12 hours.

Supplied
Priscoline Lontabs, 80 mg.
(15 mg. outer shell, 65 mg. inner core).



CIBA
SUMMIT, N. J.

PRISCOLINE® hydrochloride (tolazoline hydrochloride CIBA)
LONTABS® (long-acting tablets CIBA)

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